THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

OCTOBER, 1955

## ORIGINAL ARTICLES

# CLINICAL STUDIES ON A VASOPRESSOR AGENT: METARAMINOL (ARAMINE).* II. OBSERVATIONS ON ITS USE IN THE MANAGEMENT OF SHOCK

By MAX H. WEIL, M.D.
RESEARCH FELLOW IN MEDICINE

(From the Department of Medicine, University of Minnesota Medical School and the Medical Service, University Hospitals, Minneapolis, Minnesota)

THE present study was undertaken to assess the vasopressor agent, metaraminol in the management of shock. "Shock" is a descriptive term for a clinical sequence of events, the physiological causes of which remain obscure. The manifestations of severe prostration with hypotension, which usually include pallor, cold and moist skin, collapsed superficial veins, and altered mental status, have been recognized for centuries[1]. Current interpretations of shock are expressed as a concept of generalized vasomotor collapse that follows depletion of the circulating blood or plasma volume[12]. A differentiation is often attempted between "medical" and "surgical" shock. Medical shock is usually defined in terms of a loss of circulating fluid due to a pooling or stagnation of blood in paralyzed, dilated visceral and peripheral blood vessels. The precise locus of pooling is disputed[13,32]. In the case of surgical shock, actual loss of some blood or plasma occurs through an area of injury[4]. It is apparent that these concepts have limited utility since other factors such as dehydration, infection, and neurological injury cause and complicate shock through a combination of mechanisms.

While the state of shock is progressive, it is reversible, at least up to some point, and it is this feature which merits particular therapeutic attention. There is general agreement that when blood is lost from the intravascular compartment, or when pooling takes place in distended peripheral vessels, venous return to the heart becomes deficient. This results in inadequate ventricular filling and a fall in cardiac output[37]. As the stroke volume falls the arterial blood pressure cannot be maintained. Coronary blood flow is in turn decreased and in elderly patients myocardial infarction may occur[9]. Insufficient coronary blood flow leads to defective myocardial contractility[7]. Therefore, cardiac output is further decreased and arterial blood pressure

*Metaraminol was generously supplied by the Medical Research Division of Sharp & Dohme, Division of Merck & Co., Inc.

continues to fall. These features lead to additional stagnation and pooling, and a further reduction in venous return. A vicious cycle is begun.

The therapeutic value of vasopressor agents has been attributed to their vasoconstrictive action on "paralyzed" small blood vessels. As vascular tonus is restored, the pooled blood is recirculated[34]. Venous return to the heart is increased and better ventricular filling permits a significant rise in cardiac output. With increased cardiac output and drug-induced vasoconstriction, blood pressure is elevated; coronary blood flow is improved; and myocardial contractility is restored[29,30]. Moreover, vasopressor agents such as noradrenalin (Levophed) and metaraminol have been shown by Sarnoff and his group[29] to act directly on ventricular muscle fibers, and to produce a cardiotonic effect in a way similar to that obtained with the digitalis glycosides.

Vasopressor agents have gained wide acceptance in counteracting hypotension, which is the most constant, though not an absolute, feature of shock. With the rise in blood pressure, the patient's general appearance improves; lethargy gives way to a rational and alert state of awareness; the critically reduced urine output is usually significantly increased; and the pulse readjusts to a slower rate and fuller volume. The manifestations of shock are reversed by the administration of these substances, but if vasopressor support is withdrawn before the mechanism or mechanisms that precipitated shock are reversed, hypotension, pallor, lethargy and anuria promptly recur.

Indications for vasopressor agents have multiplied rapidly, and their applicability is included in all states of shock regardless of the primary cause. In oligemic states, initial therapy is directed at quantitative blood replacement; pressor agents are useful for subsequent support. Surgical opinion formerly held that vasoconstriction was already maximal in surgical shock, and pressor substances would serve only to further aggravate a critical vasomotor defect. Recent evidence is to the contrary. With the use of metaraminol, Sarnoff and Kaufman[31] demonstrated a notable reduction of fatalities in dogs subjected to hemorrhagic shock. Instances of apparently "irreversible" oligemic shock have been reversed by the administration of norepinephrine without apparent ill effects[6,18,25]. The use of pressor amines in shock due to myocardial infarction has had general acceptance[10,14,15]. Recommendations for pressor drugs in the treatment of shock due to pulmonary artery embolization[19], septicemia[5,38], physical trauma, anesthesia, and sympathectomy[13,23,28] have been abundantly recorded.

In our clinics, unexpected survival from shock after therapy has been observed in instances of septicemia, severe infection complicating occult hypopituitarism, extensive brain damage due to trauma, and in recurrent myocardial infarction. In each of these instances examples are available of successful long-term vasopressor treatment for periods, sometimes exceeding 2 weeks.

The applicability of vasopressor therapy to all types of shock suggests a common physiological denominator. The phenomenon of irreversibility, which has likewise been observed in all states of shock, would indicate a single final common mechanism. On the basis of evidence available, myocardial damage is regarded as this common factor. Wiggers and his co-workers[37] have demonstrated decreased work capacity of the ventricular musculature in dogs subjected to oligemic shock. Kohlstaedt and Page[17] reported an increase in the size of the heart during shock, which was attributed to

early myocardial failure. Emerson and Ebert[11] observed frank heart failure with pulmonary edema in irreversible and terminal surgical shock seen in patients during World War II. The apparent reversibility of "irreversible" shock by coronary artery perfusion in the dog has been demonstrated by Case[8] and by Sarnoff and co-workers[30]. Electrocardiographic[16,22] and pathological[21,24] evidence of myocardial damage during and following shock has been documented. Wiggers[37] and Bing[3] have discussed the importance of the coronary circulation and myocardial depression in the causation of shock. Though the initiating factor in shock may be "medical or surgical," the coronary circulation and myocardial nutrition may represent the vulnerable link in the cycle and account for its reversibility. Since vasopressor agents such as norepinephrine and metaraminol have been shown to increase effectively coronary blood flow and myocardial contractility, their use in conditions associated with shock seems to be indicated. The reversibility of shock is favored by prompt and effective vasopressor therapy, presumably through its support of myocardial function, while the factors responsible for shock are eliminated or corrected.

On the basis of preliminary observations, metaraminol approximated the requisites of an "ideal" pressor agent more closely than other commonly used vasopressor agents. Metaraminol is a potent pressor amine with prolonged duration of action and without specific effect on cardiac output[20]. Coronary blood flow is increased[29]; renal blood flow in normotensive dogs is only slightly decreased, especially, when compared to the more marked decrease caused by norepinephrine[26]; and tachyphylaxis has not been observed. Metaraminol is effective and safe when given by subcutaneous and intramuscular routes in contrast to the serious local ischemic effects, necrosis, and slough produced by extravenous norepinephrine. This drug has a prolonged duration of action, a single subcutaneous dose acting up to 1½ hours. Irregularities of the pulse, bradycardia, and electrocardiographic changes have been caused by a vagotonic action, which can be effectively blocked by atropine without altering the pressor effect[35].

PHARMACOLOGY. Metaraminol is a soluble, white-crystalline substance, and stable as a dry powder. As a member of the sympathomimetic beta phenylethylamine group, it is a close structural relative of epinephrine, norepinephrine, and methoxamine (Vasoxyl). Effective by oral and parenteral routes, it is long-acting, presumably because of its structural insusceptibility to the actions of phenol and amine oxidases[2,36]. The toxic dose for humans has not been established, but in the absence of complications from severe arterial hypertension, it is far beyond the average therapeutic range. The $LD_0$ for mice is 15 mg./kg. and $LD_{50}$ is 39 mg./kg. Like norepinephrine, metaraminol has a primary vasoconstrictor action, and shrinks nasal mucosa effectively. It has an inhibitory effect on intestinal activity, displays a mydriatic action locally, but causes no central nervous system stimulation[2]. Moyer, Morris and Snyder[27] recently demonstrated that, following hexamethonium-induced hypotension, a notable decrease in cerebral blood flow and cerebral anoxia were effectively reversed with metaraminol.

**Methods of Evaluation.** PATIENTS. Metaraminol was employed in the treatment of 61 patients suspected of having shock. However, 7 of the 61 patients were subsequently regarded as being only hypotensive, without having unequivocal shock. Twelve of the remaining patients received metaraminol for

less than 4 hours, and included moribund patients, who were near terminus at the time treatment was initiated, and patients who displayed very transient symptoms of shock, such as were seen after spinal anesthesia. The remaining 42 patients had unequivocal shock, which constituted the major group for study. Patients were, except for the manifestation of shock, unselected from the general hospital population of the University of Minnesota Hospitals, the Minneapolis General Hospital, the Veterans Administration Hospital in Minneapolis and the Ancker Hospital in St. Paul. Medical services contributed 64%, and the surgical services 36% of the total patients. The age range was 12 to 84 years, and the median age was 61 years.

ADMINISTRATION OF METARAMINOL. In profound shock, a single intravenous injection of 3 to 15 mg. of metaraminol usually produces a prompt rise in blood pressure within 2 minutes, which reaches a maximum in 5 minutes, and a pressor effect, which continues for 25 minutes. In instances of venous collapse, metaraminol was injected directly into the femoral vein, a route that is almost always accessible. The delay and trauma of a cut-down procedure was thereby avoided. After the single injection into the femoral vein, the peripheral pressure improved so that a needle could then be inserted into an antecubital vein for the continuous infusion of 30 to 200 mg. metaraminol per liter of fluid. In regulating the speed of administration, it became important to recognize that an increment in dosage was not fully reflected in the pressure response until 5 to 8 minutes after the infusion was initiated.

When the blood pressure was well maintained and the requirement for metaraminol did not exceed 20 mg. per hour, subsequent support was afforded by intermittent administration. Since a prolonged effect is achieved by subcutaneous or intramuscular injection, it proved practical to maintain blood pressure by single injections of 3 to 25 mg. repeated every one-half to 2 hours. The level of blood pressure, and the response in terms of alertness, color, and strength served as guides to dosage and the frequency of administration. Blood pressures were evaluated every 15 minutes, whenever possible, and marked fluctuations in pressure were subsequently minimized by giving an injection just before a decline was anticipated. Decreased need for medication was made evident by the accelerated response to a given dose. Small, but progressive falls in the blood pressure, required prompt increases in dosage in order to avoid a precipitous fall. When a gradual decrease in response to a given dosage was not evaluated carefully, the blood pressure sometimes suddenly fell to a low level, and intravenous administration was then necessary to regain control.

Modifications of the routes of administration were employed, such as the use of only intravenous drip, or subcutaneous and intramuscular injections, without previous intravenous therapy. In each case, the therapy was guided by the severity of the shock, and the response to treatment.

**Results.** The results of therapy for the entire group of patients are summarized in Table 1. "Prompt initial response" was defined in terms of a quick establishment of a systolic blood pressure of 100 mm. Hg or over. "Satisfactory maintenance" indicated a sustained pressor response of 100 mm. with corresponding clinical improvement. With respect to the group in shock, it is seen that 86% responded promptly, and that 76% of these patients were supported satisfactorily for periods exceeding 4 hours. Over 65% recovered from shock with the blood pressures stabilized at satisfactory levels, when vasopressor therapy was discontinued. Only 38% survived ultimately. Death occurred, on the average, 9.5 days after the beginning of therapy. The average daily dose of metaraminol was 240 mg., and the highest daily dose given to a patient who recovered was 450 mg., which was administered subcutaneously. The average total dose was 1,160 mg. given over a period of 4.5 days. The highest dose was 7,020 mg. given over a period of 28 days, principally by the subcutaneous route, to a patient who recovered from pneumonia, and who had associated adrenocortical insufficiency. The major routes of administration were subcutaneous in 44% of the cases; intravenous drip for 25%; intravenous injections for 17%; and intramuscularly for 14%.

The pre-treatment average blood

pressure was 68/57 mm. Hg, and after the initial response, 120/76 mm. Intravenous infusion permitted the control of blood pressure with the least fluctuation, and the resulting prolonged action prevented precipitous falls when the needle became dislodged from the vein (Fig. 1). The subcutaneous and intramuscular routes were of no avail in the initial control of severe shock, whereas these routes gave satisfactory results after stabilization by intravenous medication (Fig. 2). When the blood pressure was only moderately depressed, as was the case in several patients with myocardial infarction, the subcutaneous route permitted adequate control without prior intravenous therapy. No tachyphylaxis was noted during these studies. The sub-

TABLE 1.—RESULTS OF THERAPY

| | *Shock* | | *Hypotensive* | | *Transient or Terminal Shock* | | *Total* | |
|---|---|---|---|---|---|---|---|---|
| | *No.* | *%* | *No.* | *%* | *No.* | *%* | *No.* | *%* |
| Total number of patients treated | 42 | 100 | 7 | 100 | 12 | 100 | 61 | 100 |
| Patients having a prompt initial response to therapy | 36 | 85.7 | 6 | 85.7 | 9 | 75 | 51 | 83.6 |
| Patients in whom blood pressure was satisfactorily maintained | 32 | 76.1 | 5 | 71.4 | 3 | 25 | 40 | 65.5 |
| Patients recovering from shock | 28 | 66.6 | 5 | 71.4 | 6 | 50 | 39 | 64 |
| Patients with ultimate recovery and discharge from the hospital | 16 | 38.1 | 3 | 42.8 | 2 | 16.6 | 21 | 34.4 |

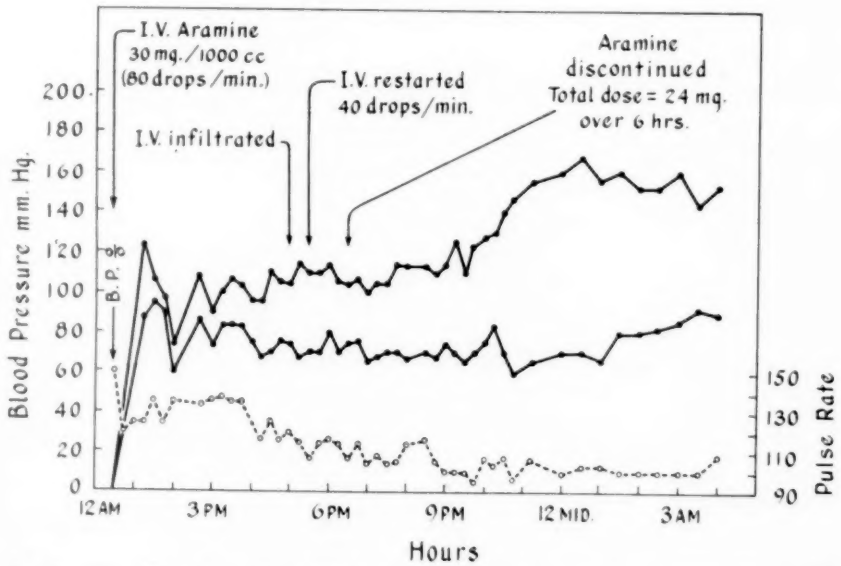


Fig. 1.—Pressor effect of metaraminol in a 57-year-old man, operated upon for removal of brain tumor, who developed pneumonia and shock 36 hours after craniotomy. Patient recovered from shock but died of neurological causes 42 days later.

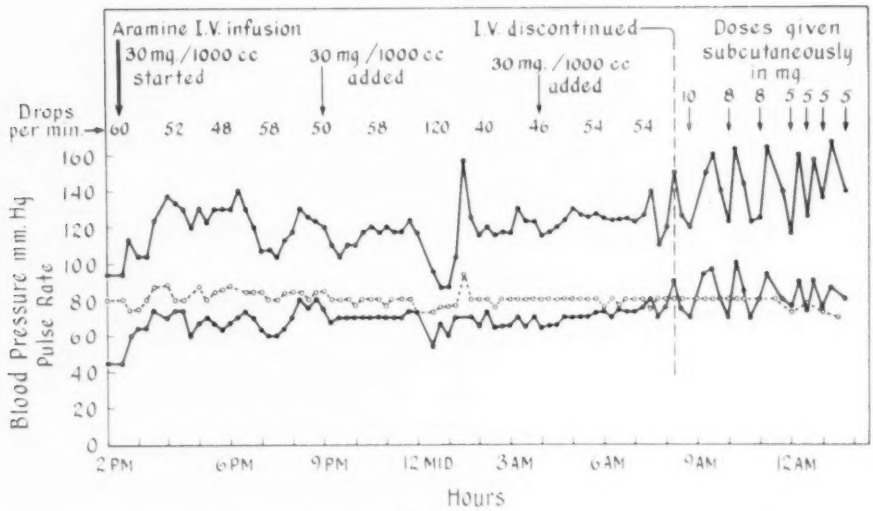


Fig. 2.—Pressor effect of metaraminol in a 67-year-old man with shock due to Proteus septicemia. After 3 days of continuous therapy with norepinephrine (Levophed), thrombophlebitis and skin discoloration occurred at the infusion site. Metaraminol was substituted at the time indicated and maintained, first by intravenous and then by subcutaneous route, for 3 days, with final recovery.

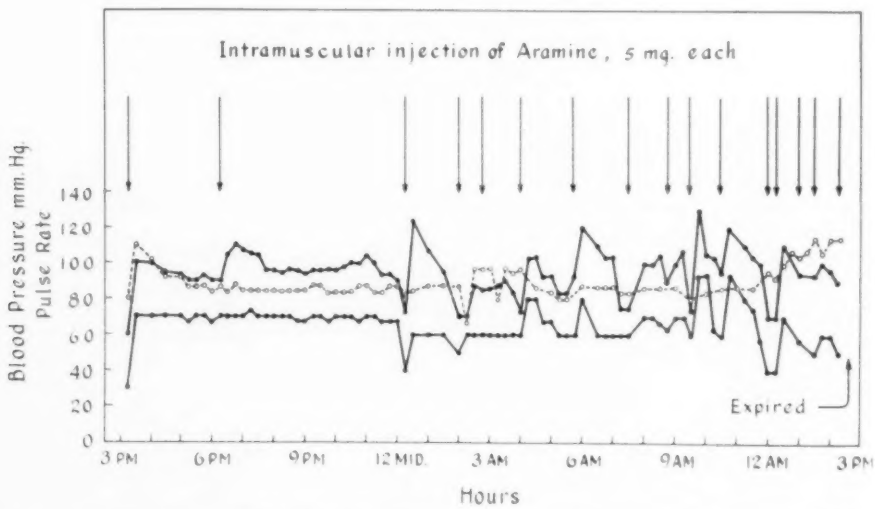


Fig. 3.—Pressor effect obtained with intermittent intramuscular injection of metaraminol in a 30-year-old diabetic male dying of renal failure and multiple foci of infection. Although normotensive levels were not achieved, vasomotor collapse and impaired consciousness were reversed and the patient was able to converse until shortly before death.

cutaneous route was generally preferred over the intramuscular route because earlier data demonstrated the same pressor effect over a greater period of time[35]. But the intramuscular route was also feasible (Fig. 3).

The majority of patients included in the group with shock was represented by coronary thrombosis, or myocardial infarction, and infectious diseases with and without demonstrable septicemia. The results of therapy for the different groups of diseases are summarized in Table 2. The results for each of the 42 patients in the group with shock are summarized in Table 3.

TABLE 2.—RESULTS OF SHOCK THERAPY FOR VARIOUS STATES

| *Diagnosis* | *No.* | *Prompt Initial Response* | *Satisfactory Maintenance* | *Recovery from Shock* | | *Total Recovery* | |
|---|---|---|---|---|---|---|---|
| | | | | *No.* | *%* | *No.* | *%* |
| Coronary thrombosis and myocardial infarction | 16 | 15 | 13 | 9 | 56.2 | 6 | 37.5 |
| Septicemia | 6 | 4 | 3 | 4 | 66.6 | 2 | 33.3 |
| Infection without evidence of septicemia | 9 | 9 | 7 | 6 | 66.6 | 3 | 33.3 |
| Reaction to drugs or to blood transfusions | 3 | 3 | 3 | 3 | 100 | 3 | 100 |
| Vascular accidents (thrombotic and embolic) | 3 | 2 | 3 | 2 | 66.6 | 0 | 0 |
| Following surgery on the adrenal glands | 3 | 2 | 1 | 2 | 66.6 | 2 | 66.6 |
| Miscellaneous | 2 | 2 | 2 | 2 | 100 | 0 | 0 |

SIDE EFFECT AND TOXICITY. Marked diaphoresis was commonly observed. In several patients, the skin remained cold and clammy, although other evidences of shock had subsided. Two patients had prolonged singultus, which was doubtfully related to metaraminol administration. Generalized urticaria occurred in one patient after subcutaneous administration, but the rash disappeared after one hour, and did not recur on subsequent administration. Auscultatory bigeminy was noted in 2 female patients, and coupled rhythm due to premature ventricular contraction was confirmed electrocardiographically in one of these patients. Both of these patients were receiving corticosteroids following adrenal gland surgery and demonstrated augmented pressor response to metaraminol. Two elderly patients were maintained on as little as 1 mg. of metaraminol, after shock was controlled, because of increased sensitivity to the pressor effect. Bradycardia, prominent in normotensive volunteers, was uncommon[35]. A single injection of 50 mg. of metaraminol given intravenously in the case of an unresponsive patient in profound shock was followed by localized convulsive movements lasting for one minute.

COMPARISON WITH OTHER VASOPRESSOR AGENTS. Of the total group of 61 patients, 24 were also treated with other vasopressor agents and their effects were compared. Norepinephrine gave a pressor response in 5 patients after metaraminol therapy was unavailing. Four of these 5 patients ultimately died. In the survivor, metaraminol was used only by the subcutaneous route, so that comparison with the intravenous route of administration of metaraminol was not established. Methoxamine (Vasoxyl) in a dosage of 20 mg. intramuscularly achieved a less satis-

TABLE 3.—DATA ON 42 PATIENTS WITH SHOCK TREATED WITH METARAMINOL

| Patient No. Age & Sex | Primary Disease | Blood Pressure: Before Treatment | Blood Pressure: After Treatment | Major Route of Adm. | Hours of Treatment | Total Dose in mg. | Initial Response | Maintenance | Recovery from Shock | Final Recovery | Other Agents Used |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1<br>63 M | Pyelonephritis; septicemia due to *Proteus vulgaris* | 60/45 | 160/80 | Subc. | 432 | 4496 | Good | Fair | Yes | Yes | |
| 2<br>57 M | Brain tumor with possible septicemia. Postoperative bronchopneumonia | 0/0 | 122/88 | I.V.Drip | 6½ | 24 | Good | Good | Yes | No | |
| 3<br>82 M | Purulent bronchitis. Generalized arteriosclerosis. | 50/24 | 135/74 | I.V.Drip | 28 | 90 | Good | Good | Yes | No* | Norepinephrine |
| 4<br>56 M | Brain tumor compressing midbrain. | 88/80 | 104/80 | I.V.Drip | 24 | 635 | Good | Good | Yes | No* | |
| 5<br>50 M | Coronary thrombosis and heart failure. Postoperative jejunocardiorrhaphy. | 80/50 | 104/54 | I.V.Drip | 22 | 1185 | Good | Fair | No | No* | |
| 6<br>52 F | Metastatic carcinoma of breast. Postoperative adrenalectomy. | 0/0 | 94/70 | I.V. injection | 24 | 1810 | Fair | Fair | No | No* | Norepinephrine |
| 7<br>51 M | Myocardial infarction. | 85/60 | 170/110 | I.M. | 240 | 1188 | Good | Good | Yes | Yes | |
| 8<br>58 F | Myocardial infarction. | 70/60 | 112/90 | Subc. | 24 | 245 | Good | Good | No | No* | |
| 9<br>45 M | Accidental subcutaneous injection of Varidase. | 64/0 | 132/70 | I.V.Drip | 62 | 505 | Good | Good | Yes | Yes | |
| 10<br>51 M | Postoperative jejunocardiorrhaphy. Myocardial infarction. | 70/28 | 130/70 | I.V.Drip | 56 | 625 | Good | Good | Yes | No* | |
| 11<br>28 F | Postoperative adrenal exploration. | 80/60 | 114/70 | I.V. injection | 16 | 150 | Good | Fair | Yes | Yes | |
| 12<br>57 M | Shock following administration of chlorpromazine. | 50/0 | 108/70 | I.V.Drip | 48 | 332 | Fair | Good | Yes | Yes | |
| 13<br>47 M | Duodenal ulcer with perforation. | 88/72 | 140/72 | I.V.Drip | 31 | 35 | Good | Good | Yes | No* | Methoxamine |
| 14<br>64 F | Myocardial infarction. | 0/0 | 120/70 | Subc. | 64 | 340 | Good | Good | Yes | Yes | |
| 15<br>54 M | Calcific aortic stenosis. Multiple pulmonary infarctions. | 0/0 | 100/70 | I.V.Drip | 18 | 60 | Fair | Good | Yes | No* | Norepinephrine |

* Necropsy

infarctions.

* Necropsy

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 16<br>62 F | Coronary thrombosis. Cerebral infarction. | 54/40 | 128/92 | Subc. | 18 | 280 | Good | Poor | Yes | Yes | Norepinephrine |
| 17<br>55 F | Pyelonephritis | 60/0 | 138/86 | Subc. | 12 | 55 | Good | Good | Yes | No | Norepinephrine |
| 18<br>30 M | Osteomyelitis. Necrobiosis diabeticorum. Renal insufficiency. | 60/30 | 100/70 | I.M. | 24 | 125 | Good | Good | No | No | Methoxamine |
| 19<br>61 M | Myocardial infarction. | 80/58 | 162/100 | Subc. | 288 | 1420 | Good | Good | Yes | Yes | |
| 20<br>46 M | Myocardial infarction. | 72/48 | 104/64 | Subc. | 493 | 4990 | Fair | Good | Yes | Yes | Methoxamine |
| 21<br>82 M | Possible mesenteric artery thrombosis. Possible septicemia. | 70/38 | 104/70 | Subc. | 36 | 130 | Good | Good | Yes | No | Norepinephrine |
| 22<br>76 M | Prostatic abscess. Postoperative transurethral prostatic resection. | 70/60 | 130/70 | I.V.Drip | 132 | 1390 | Good | Fair | Yes | Yes | Methoxamine |
| 23<br>62 M | Myocardial infarction. | 94/60 | 114/70 | I.V.Drip | 29 | 760 | Good | Fair | No | No* | |
| 24<br>84 M | Septicemia due to *Micrococcus pyogenes*. Purulent pericarditis. | 84/38 | 108/38 | Subc. | 60 | 370 | Fair | Good | Yes | No* | |
| 25<br>67 M | Myocardial infarction. | 74/64 | 150/100 | Subc. | 216 | 1383 | Good | Good | Yes | No | |
| 26<br>60 M | Myocardial infarction. | 60/0 | 126/70 | Subc. | 88 | 466 | Good | Good | No | No* | Neosynephrine |
| 27<br>64 M | Myocardial infarction. | 68/54 | 110/86 | I.V.Drip | 8 | 475 | Good | Good | No | No* | |
| 28<br>70 M | Postoperative cervical laminectomy. Myocardial infarction. | 50/44 | 124/72 | I.V.Drip | 240 | 1343 | Good | Good | No | No* | |
| 29<br>67 M | Postoperative transurethral prostatic resection. Septicemia due to *Proteus vulgaris*. | 92/54 | 138/80 | I.V.Drip | 60 | 256 | Good | Good | Yes | Yes | Norepinephrine |
| 30<br>76 M | Pyelonephritis. Septicemia due to *Pseudomonas aeruginosa*. | 70/40 | 120/66 | I.V.Drip | 5 | 50 | Good | Good | Yes | No* | |

TABLE 3.—DATA ON 42 PATIENTS WITH SHOCK TREATED WITH METARAMINOL—(*Continued*)

| *Patient No. Age & Sex* | *Primary Disease* | *Blood Pressure* | | *Major Route of Adm.* | *Hours of Treatment* | *Total Dose in mg.* | *Initial Response* | *Main tenance* | *Recovery from Shock* | *Final Recovery* | *Other Agents Used* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | *Before Treatment* | *After Treatment* | | | | | | | | |
| 31<br>48 F | Typhoid fever. Septicemia due to *Micrococcus pyogenes.* | 60/30 | 60/30 | I.V.Drip | 14 | 400 | Poor | Poor | No | No* | Norepinephrine |
| 32<br>63 M | Adrenal cortical insufficiency. Lobar pneumonia. | 80/40 | 162/80 | Subc. | 672 | 7020 | Good | Good | Yes | Yes | Methoxamine |
| 33<br>54 M | Septicemia due to *Micrococcus pyogenes.* | 56/48 | 108/80 | Subc. | 20 | 335 | Good | Fair | No | No | Norepinephrine |
| 34<br>56 M | Postoperative gastric resection. Pyrogenic reaction following a blood transfusion | 110/88 | 180/140 | Subc. | 76 | 185 | Good | Good | Yes | Yes | |
| 35<br>82 M | Arteriosclerotic heart disease. Femoral artery embolization. | 0/0 | 110/70 | Subc. | 8 | 185 | Good | Good | No | No | |
| 36<br>71 M | Bronchopneumonia. | 92/52 | 162/90 | I.M. | 88 | 1370 | Good | Good | No | No* | Norepinephrine<br>Methoxamine |
| 37<br>75 M | Bronchopneumonia. | 90/54 | 164/92 | Subc. | 144 | 1270 | Good | Fair | No | No* | Norepinephrine |
| 38<br>31 M | Postoperative adrenal exploration and removal of pheochromocytoma. | 82/64 | 260/160 | Subc. | 120 | 570 | Good | Good | Yes | Yes | Norepinephrine |
| 39<br>79 M | Myocardial infarction. | 72/60 | 108/70 | Subc. | 36 | 80 | Good | Good | Yes | Yes | |
| 40<br>12 F | Meningo-encephalitis due to Pneumococcus. | 50/0 | 100/60 | Subc. | 96 | 270 | Good | Good | Yes | Yes | Norepinephrine<br>Methoxamine |
| 41<br>72 M | Postoperative transurethral prostatic resection. Myocardial infarction. | 80/60 | 130/84 | I.V.Drip | 17 | 170 | Good | Good | No | No | |
| 42<br>72 M | Myocardial infarction. | 94/72 | 124/88 | Subc. | 144 | 125 | Good | Good | Yes | No* | |

* Necropsy

factory pressor response than 10 mg. of Aramine when compared in 5 patients. Intravenous administration of methoxamine was also less effective than metaraminol in smaller dosage. Phenylephrine (Neosynephrine) in equal dosage, compared in 2 patients, also produced a weaker response. The order of effectiveness of these agents in therapy of shock was noted to be norepinephrine, metaraminol, methoxamine, and phenylephrine.

**Discussion.** The definition and diagnosis of shock are based on a clinical manifestation created by different disease processes. A moderate state of shock as defined by one observer, may be moderate hypotension according to the criteria accepted by another. Studies, including the present investigation, are hampered because shock, as a clinical entity, can be described so much better than quantitated. Series of patients reported by different authors are not readily comparable in analyzing the therapy of shock. Objectivity is achieved primarily by mortality data, postulating that only patients are included who fulfill the criteria of the complete picture of shock, and not hypotension alone. In this presentation, an attempt has been made to exclude individuals in whom there was doubt as to the presence of shock. Some indication of successful therapy is derived from the reversal of the shock state with therapy. At times the least reliable, and yet the only numerical index of therapy for the individual case, is the rise in blood pressure.

As far as comparisons are possible, the results obtained in the present series with metaraminol compare favorably with those obtained with norepinephrine, and metaraminol has certain advantages. Kurland[18], reporting on 14 patients in shock due to myocardial infarction, who were treated with norepinephrine, observed a satisfactory pressor response in 64% and 29% of the patients survived. In 16 cases of shock due to miscellaneous causes, 90% had an initial pressor response to norepinephrine but only 3 or 21% survived. Miller and co-workers[25] studied 32 patients treated with norepinephrine, and cited a good initial pressor response for 78% with 37% of the patients surviving. In the present investigation, an effective initial response was recorded for 86% of the patients, and 38% survived.

Metaraminol is a valuable addition to those agents available in the treatment of shock. Excepting the two instances in which administration was followed by ventricular arrhythmias, the drug was free of undesirable side effects. The ease with which metaraminol can be given encourages its prompt use in shock. The value of this agent was particularly apparent in cases requiring prolonged pressor support. The use of subcutaneous injections at hourly intervals replaced the continuous norepinephrine drip with its hazard of infiltration and local tissue necrosis, and the almost inevitable skin sloughs that follow several days of therapy[33,34]. Because of its prolonged duration of action, the administration of metaraminol was much easier to control than norepinephrine, and did not require constant observation by nursing personnel.

Norepinephrine is a more potent pressor agent than metaraminol and will at times produce a pressor response when metaraminol will fail to do so. Ultimate survival is unlikely, however, when norepinephrine is used after failure with metaraminol. The safety and practicality of metaraminol recommends its use as the pressor amine of choice in shock. Norepinephrine should be reserved for those instances in which metaraminol given intravenously is found to be ineffective.

**Conclusions and Summary.** When blood or plasma is lost through a wound, or when dehydration or pooling in distended blood vessels cause an initial reduction in physiologically-effective blood volume, shock ensues. Inadequate venous return, decreased cardiac output, and decreased coronary blood flow follow. Myocardial insufficiency and further loss of circulatory momentum complete a vicious cycle. Vasopressor agents, such as norepinephrine (Levophed) and metaraminol (Aramine), contract the peripheral vascular bed, increase venous return and coronary blood flow, and act directly on the heart muscle to increase its contractility. These effects break this cycle and counteract physiological disturbances of late shock, regardless of its initial cause.

Metaraminol, on the basis of preliminary studies, was found to fulfill certain vasopressor "ideals" more closely than commonly used agents. Sixty-one hypotensive patients were treated with metaraminol, of whom 42 were in shock for 4 or more hours. The results of therapy were at least as satisfactory as those reported for norepinephrine. Bigeminal rhythm was noted in 2 patients treated with metaraminol and corticosteroids concurrently, although no detrimental action on cardiac rhythm was reported by previous observers. No other undesirable effects were noted.

The principal advantages of metaraminol are potent pressor action, its prolonged duration of action, the ease with which its administration can be controlled, and its availability for direct intravenous, intramuscular and subcutaneous administration. The safety and practicality of this drug recommends its use in the treatment of shock.

ACKNOWLEDGMENTS: For constant guidance, both in the initiation and in the conduct of these studies, the author is greatly indebted to Dr. W. W. Spink. The kind cooperation of Dr. J. Sproifka of Ancker Hospital, St. Paul, and Dr. A. Voigt of Minneapolis General Hospital, and the technical assistance of Miss Joan Meyer are gratefully acknowledged.

## REFERENCES

1. **Adams, F.:** The Genuine Works of Hippocrates. New York: William Wood and Co., 1886, **1**, 194 (the book of prognostics).
2. **Beyer, K. H.:** Personal communication, The Medical and Research Divisions, Sharp & Dohme, West Point, Pa.
3. **Bing, R. J.:** Ann. New York Acad. Sci., **55**, 367, 1952.
4. **Blalock, A.:** Principles of Surgical Care; Shock and Other Problems. St. Louis: C. V. Mosby Co., 1940.
5. **Braude, A. I., Williams, D., Siemienske, J.,** and **Murphy, R.:** A.M.A. Arch. Int. Med., **92**, 75, 1953.
6. **Cappe, B. E.,** and **Pallin, I. M.:** Anesthesiology, **12**, 728, 1951.
7. **Case, R. B., Berglund, E.,** and **Sarnoff, S. J.:** Circulation Res., **2**, 319, 1954.
8. **Case, R. B., Sarnoff, S. J., Waithe, P. E.,** and **Sarnoff, L. C.:** J. Am. Med. Assn., **152**, 208, 1953.
9. **Davis, H. A., Parlante, V. J.,** and **Hallsted, A. M.:** A.M.A. Arch. Surg., **62**, 698, 1951.
10. **Deterling, R. A.,** and **Apgar, V.:** Ann. Surg., **133**, 37, 1951.
11. **Emerson, C. P.,** and **Ebert, R. V.:** Ibid., **122**, 745, 1945.
12. **Frank, H. A.:** New England J. Med., **249**, 445, 1953.
13. **Goldenberg, M., Apgar, V., Deterling, R.,** and **Pines, K. L.:** J. Am. Med. Assn., **140**, 776, 1949.
14. **Griffith, G. C., Wallace, W. B., Cochran, B., Jr., Nerlick, W. E.,** and **Frasher, W. C.:** Circulation, **9**, 527, 1954.
15. **Hellerstein, H. K., Brofman, B. L.,** and **Caskey, W. H.:** Am. Heart J., **44**, 407, 1952.
16. **Izquieta, J. M.,** and **Pasternack, B.:** Proc. Soc. Exp. Biol. & Med., **61**, 407, 1946.
17. **Kohlstaedt, K. G.,** and **Page, I. H.:** Surgery, **16**, 430, 1944.
18. **Kurland, G. S.,** and **Malach, M.:** New England J. Med., **247**, 383, 1952.

19. **Livesay, W. R.,** and **Chapman, D. W.,:** Am. J. M. Sci., **225,** 159, 1953.
20. **Livesay, W. R., Moyer, J. H.,** and **Chapman, D. W.:** Am. Heart J., **47,** 745, 1954.
21. **Mallory, T. B.:** J. Mt. Sinai Hosp., **16,** 137, 1949.
22. **Master, A. M., Dack, S., Horn, H., Freedman, B. I.,** and **Field, L. E.:** Circulation, **1,** 1302, 1950.
23. **Mayer, R. A.,** and **Ruben, J. E.:** J. Phila. Gen. Hosp., **2,** 115, 1951.
24. **Melcher, G. W., Jr.,** and **Walcott, W. W.:** Am. J. Physiol., **164,** 832, 1951.
25. **Miller, A. J., Shifrin, A., Kaplan, B. M., Golde, H., Billings, A.,** and **Katz, L. N.:** J. Am. Med. Assn., **152,** 1198, 1953.
26. **Moyer J. H.,** and **Handley, C. A.:** Am. Heart J., **48,** 173, 1954.
27. **Moyer, J. H., Morris, G.,** and **Snyder, H.:** Circulation, **10,** 265, 1954.
28. **Poe, M. F.:** Anesthesiology, **15,** 547, 1954.
29. **Sarnoff, S. J., Case, R. B., Berglund E.,** and **Sarnoff, L. C.:** Circulation, **10,** 84, 1954.
30. **Sarnoff, S. J., Case, R. B., Waithe, P. E.,** and **Isaacs, J. P.:** Am. J. Physiol., **176,** 439, 1954.
31. **Sarnoff, S. J.,** and **Kaufman, H. E.:** Circulation Res., **2,** 420, 1954.
32. **Stead, E. A., Jr.:** Shock Syndrome in Internal Medicine in Oxford Medicine (Edited by Henry A. Christian). New York: Oxford University Press, **2,** 133, 1945.
33. **Uricchio, J. F., Calenda, D. G.,** and **Cutts, F. B.:** J. Am. Med. Assn., **152,** 607, 1953.
34. **Von Euler, M. S.:** Ann. Int. Med., **41,** 699, 1954.
35. **Weil, M. H.,** and **Spink, W. W.:** Am. J. Med. Sci., **229,** 661, 1955.
36. Iidem: Clinical Studies on a Vasopressor Agent, Metaraminol. III. Observations on Its Oral Use. Unpublished.
37. **Wiggers, C. J.:** Physiology of Shock. New York: Commonwealth Fund, 1950.
38. **Wise, R. I., Shaffer, J. M.,** and **Spink, W. W.:** J. Lab. & Clin. Med., **40,** 961, 1952.

## CONCLUSIONES E SUMMARIO IN INTERLINGUA

### Studios Clinic Super un Agente Vasopressor: Metaraminol (Aramina) II. Observationes Super su Uso in le Tractamento de Choc

Quando sanguine o plasma es perdite via un vulnere, o quando dishydratation o accumulationes in distendite vasos sanguinee resulta in un reduction initial del physiologicamente efficace volumine de sanguine, le effecto es le occurrentia de choc. Seque inadequate retorno venose, reduction del volumine-minuta del corde, e diminution del fluxo sanguinee coronari. Le consequente insufficientia myocardiac e le perdita additional de momento circulatori completa un cyclo vitiose. Agentes vasopressor, como norepinephrina (Levophed) e metaraminol (Aramina), contrahe le peripheric rete vascular, augmenta le retorno venose e le fluxo sanguinee coronari, e age directemente super le musculo cardiac de maniera a augmentar su contractilitate. Iste effectos disrumpe le cyclo describite e contraveni disturbationes physiologic que resulta del choc, sin reguardo a que esseva su causa initial.

Super le base de studios preliminari il pareva que metaraminol satisface certe "ideales" vasopressor plus completemente que le agentes in uso currente. Esseva tractate con metaraminol 61 patientes hypotensive, includente 42 in stato de choc durante 4 horas o plus. Le resultatos therapeutic esseva al minus tanto satisfacente como illos reportate pro norepinephrina. Un rhythmo bigeminal esseva notate in 2 patientes tractate simultaneemente con metaraminol e corticosteroides, ben que previe observatores non habeva reportate un action detrimentose super le rhythmo cardiac. Nulle altere effectos negative esseva notate.

Le avantages principal de metaraminol es su potente action pressorial, le prolongate duration de su action, le facilitate del regulation de su administration, e su disponibilitate pro administrationes directemente intravenose, intramuscular, e subcutanee. Le qualitates practic e non-riscose de iste droga recommenda su uso in le tractamento de choc.

# EVALUATION OF SKIN TESTING METHODS EMPLOYED IN THE DIAGNOSIS OF PENICILLIN ALLERGY

By Louis Tuft, M.D.
CLINICAL PROFESSOR OF MEDICINE (IMMUNOLOGY)

Donald C. Gregory, B.A.

AND

Joan Gregory, B.S., M.T.

(From the Clinic of Allergy and Applied Immunology, Temple University Hospital and School of Medicine, Philadelphia, Pennsylvania)

The value of penicillin in the treatment of various infections is well established. But, as pointed out recently by Kern and Wimberley[4], its widespread and sometimes injudicious use has resulted in an increasing number of allergic reactions. Some of these have been quite severe, prolonged or incapacitating, and even fatal. As a matter of fact, penicillin probably ranks today as one of the most common causes of allergic reactions to drugs.

Even though the incidence of reactions to penicillin is comparatively small, when one considers the enormous amount being administered daily, nevertheless the increasing severity of some of the reactions and the danger of ensuing fatality make it highly desirable to prevent their occurrence. Clinicians aware of this possibility have attempted to find out in individual patients about to receive penicillin whether they were allergic to the drug. Unfortunately, as indicated by a review of the literature on this subject, there is no agreement as to how this can be accomplished and especially as to which test* should be employed for that purpose. No two authors seem to agree either upon the method, upon the concentration used, or the dosage. Thus, for example, Peck *et al.*[7] in one of the earliest reports upon this subject, suggested that the presence of existing sensitivity should be determined upon the basis of a delayed positive test read at 24 and 48 hours. One obvious objection to this is that such a delay in a patient requiring penicillin is impractical, especially since the test is likely to reveal sensitivity in only a small percentage of patients. But even more important, it is highly doubtful whether a test which depends upon the delayed or tuberculin type of reaction is a proper indicator for penicillin allergy. The latter, as with horse serum allergy, usually is of the anaphylactic type and depends for its detection upon the immediate, urticarial or whealing type of reaction. Similar objections apply to the use of the patch test which likewise has been suggested as a means of detection. This test also depends upon a delayed type of reaction and is useful only in the contact form of allergic dermatitis to penicillin.

Despite these suggestions, in those reported instances where tests were

*Since the word "reaction" is applied in its common usage both to the positive skin test reaction and to the generalized allergic reaction seen after penicillin administration, its use for both in this article might cause confusion. To avoid this, we will speak of the skin test reaction as a positive or negative test and limit the word reaction to that seen after injection.

done, the authors usually employed either the scratch or intracutaneous technique. However, there was no uniformity in the material, amount, or concentration of penicillin which was employed in doing the tests; and as a rule, no control test was done. The wide variation in methods utilized for the attempted diagnosis of penicillin allergy is illustrated in Table 1 containing a selected list of published articles on penicillin reactions. Inspection of the table, as well as review of the extensive literature on this subject, emphasizes that there is at present no standard method of skin testing for penicillin allergy. Even if such a test were available, considerable doubt exists, as indicated in numerous publications, as to the diagnostic value of any skin testing procedure. Thus, for example, Kern and Wimberley[4] in their review point out that the incidence of positive skin tests is likely to be small and that allergic reactions may occur despite a negative skin test.

TABLE 1.—TESTS AND TECHNIQUES ADVOCATED FOR DETECTION OF PENICILLIN SENSITIVITY

| *Author* | *Year* | *No. of Cases* | *Type of Test* | *Concentration in Units per cc.* | *Amount in cc.* |
|---|---|---|---|---|---|
| Kolodny & Denhoff[5] | 1946 | 124 | Intracut. | 1,000 or 2,000 | 0.1 |
| | | | Eye | ? | 1 drop |
| Hopkins & Lawrence[2] | 1947 | 618 | Intracut. | 1,000 to 10,000 | 0.1 |
| | | | Patch | 100,000 | |
| Peck *et al*[7] | 1948 | 406 adults | Intracut. (immed.) | 5,000 | 0.01–0.02 |
| | | 91 children | Intracut. (delayed) | 20,000 | 0.1 |
| | | | Patch | 2,000, 100,000 | |
| Risman and Boger[3] | 1950 | 600 | Intracut. | 2,000 | 0.1 |
| Kadison *et al*[1] | 1951 | 20 | Intracut. | 1,000 | 0.1 |
| Mayer *et al*[6] | 1953 | 6 | Intracut. | 1,000 | 0.01 |
| Feinberg *et al*[1] | 1953 | . . . | Intracut. | 5 to 5,000 | 0.01 |
| | | | Scratch | 50,000 to 100,000 | 1 drop |
| Kern & Wimberley[4] | 1953 | . . . | Intracut. (both immed. & delayed) | 5,000 | 0.02 |
| | | | Scratch | ? | 1 drop |
| | | | Patch | 50,000 | |

Because of the lack of standardization of the testing methods hitherto employed in the diagnosis of penicillin allergy and the uncertainty as to their value, it seemed worth while to conduct an investigation designed to evaluate the various types of tests now being employed, and to determine, if possible, their usefulness. The results obtained form the basis of the present report.

**Material and Methods.** Since intracutaneous tests could not be done with oily materials, aqueous mixtures were used in the present study. This included two types of penicillin and their vehicles. The materials were as follows: 1. Wycillin, procaine penicillin G in aqueous suspension; 2. Bicillin (dibenzyl penicillin), dibenzylethylenediamine dipenicillin G in aqueous suspension; 3. Wycillin and Bicillin vehicle, composed of a mixture of carboxymethylcellulose, sodium citrate, methylparaben and propylparaben. The same solution was used as a vehicle for both types of penicillin in doing the control tests even though during the course of the investigation, they were labelled as "Wycillin vehicle" and "Bicillin vehicle."

Intracutaneous tests were performed in the same way as with other allergenic extracts; namely, by the intracutaneous injection of 0.02 cc. of the penicillin solution into the outer surface of the arm, the reaction being read after a lapse of 10 minutes.

Scratch tests were performed by placing one drop of penicillin solution on a small linear scratch (¼" in length) made through the epidermis of the volar surface of the forearm, the reaction being read after 20 minutes. Both the scratch and intracutaneous

tests were done with concentrations of Bicillin and Wycillin, varying from 100 units per cc. to 300,000 units per cc. In the earlier tests when we were still trying to find out which concentration would be safe, we started with concentrations of 100 units per cc. and worked up gradually. However, subsequent experience indicated that much higher concentrations were safe so that our later scratch tests were carried out with concentrations of 10,000 to 300,000 units per cc.

Patch tests were done with both Bicillin and Wycillin in a concentration of 300,000 units per cc. Small squares of linen were saturated with these solutions and applied directly to the skin of the arm under a protective adhesive patch. The patch was removed after 48 hours and the reaction noted. In all patients tested by the scratch or intracutaneous tests, control tests were done with the corresponding vehicle. Likewise in all these patients, the sites were inspected not only for immediate reactions but also after 24 and again after 48 hours to detect the presence of delayed reactions.

The patients utilized for these studies included patients seen in the Outpatient Medical and Obstetrical Clinics* and Wards of Temple University Hospital* and also inmates of the Veterans Administration Hospital at Coatesville, Pennsylvania.* Before performing any tests on these individuals an attempt was made to find out either from the patient or from hospital records, if available, information concerning the previous administration of penicillin, keeping in mind that it could have been given not only by injection but also orally either in the form of tablets or troches. A special attempt was made to find out whether an allergic reaction had followed the penicillin administration and if so, the date of its occurrence. In all patients, regardless of reaction, an attempt also was made to obtain a history of major allergy (for example, asthma or hay fever, or both) in the patient or his family; also a history of skin disorders, notably ringworm, in the patient.

For purposes of analysis, the patient material utilized in these studies can be divided into 3 groups: 1) Individuals who so far as we could determine from the history, never had received penicillin. This was considered the control group and totaled 134 individuals. 2) Individuals with a history of previous penicillin administration but no known subsequent allergic reaction. This group comprised 463 patients. 3) Individuals who received penicillin and subsequently developed an allergic reaction. This included 32 patients.

The actual method of procedure utilized in the individual patient was as follows: Since we considered it unlikely that the patients in the control group would have a positive skin test reaction to penicillin, we omitted the initial scratch tests and tested them intracutaneously with varying concentrations of Bicillin and Wycillin and with the undiluted vehicle. But if a positive test was obtained in any patient, a scratch test then was performed in the manner already indicated. On the other hand, the earlier patients in Groups 2 and 3 were tested both by the scratch and intracutaneous methods with both Wycillin and Bicillin in increasing concentrations as well as with the vehicle (undiluted). However, the scratch tests proved so uniformly negative on the first series of patients tested, that they were omitted subsequently except on the patients' in Group 3 with a history of previous reaction in whom both tests were done. The procedure followed was to do the scratch and intracutaneous tests with increasing strengths either until a positive was obtained or until the highest concentration was reached. As with all the tests done, whenever an immediate positive test was obtained, the site was inspected again at 24 and 48 hours to see if a delayed positive test followed. Finally, because the question arose as to whether it was necessary to use freshly prepared solutions of penicillin for each series of skin tests, we attempted to determine the stability of the solutions by testing patients giving positive skin tests both with a freshly prepared penicillin solution and also with the same concentration of solutions which had been kept both at room temperature and in the refrigerator for varying periods of time.

**Results.** Altogether in the 3 groups, a total of 629 patients were studied. Of the 134 patients in the control group tested intracutaneously, one had a positive skin test in slight degree to Wycillin in a concentration of 300,000 units per cc. with negative tests to Bicillin and to both vehicles and with no delayed positive test. Subsequent scratch

*The authors are greatly indebted to the many staff physicians and others at both institutions for their gracious cooperation in providing us with the patient material; also to Wyeth Laboratories both for the penicillin solutions used and for the grant-in-aid which made this investigation possible.

test with Wycillin in similar concentration also was positive. This patient had an active ringworm infection, was asthmatic and as nearly as she could remember had not received penicillin previously.

Intracutaneous tests with a single vehicle were done on all patients in the control group, some being tested with what was labelled as the "Wycillin vehicle" and others with the "Bicillin vehicle." Thus, of 87 tested intracutaneously with the latter, slight positives were obtained in 4, whereas of the 47 tested with the "Wycillin vehicle," 3 were positive, also slight in degree. Since both vehicles were the same solution, this means that of 134 patients tested with the vehicle, 7 were positive in slight degree.

Because we considered it unlikely that the patients in the control group would show evidence of sensitivity, no patch tests were done upon members of the control group.

Intracutaneous tests with both Bicillin and Wycillin were done on 463 patients in Group 2. All of these patients were tested with either its correspondingly labelled vehicle alone or in some instances with both. Scratch tests were done on 77 patients in this group. Of the 463 patients tested intracutaneously, 9 had positive tests to the Wycillin or Bicillin, or both. Subsequent scratch tests done on these 9 patients using a concentration of 100,000 units per cc. also were negative and no delayed positives were observed. The data relating to these 9 patients in Group 2 are summarized in Table 2. It will be noted at once that patient No. 7 had positive tests in slight degree to Bicillin 300,000 units per cc. and to its vehicle. Such a positive test, therefore, must be considered nonspecific. This also applies to patient No. 8 and to patient No. 9. Therefore, of the 9 patients with positive tests, only 6 can be considered as having specific positive tests to penicillin. Of the 6, the sensitivity seemed rather definite and strong in patient No. 2, who said she had received penicillin some time in the past without subsequent reaction but did not recall the date. In this patient it is to be noted that there was a progressive increase in the strength of the reaction beginning with the 100 unit concentration up to the 10,000 unit concentration. Since this patient had a positive test in approximately the same degree to the varying concentrations of both Bicillin and Wycillin and negative tests to the vehicle, the results indicate that this patient had a specific sensitivity to the penicillin itself rather than to any of the components in the mixture. It is interesting also to note that this patient had negative scratch tests to both Bicillin and Wycillin despite definite positive intracutaneous tests, emphasizing the superior sensitiveness of the intracutaneous method. Likewise, this patient did not show a delayed positive reaction after 48 hours such as would be expected if the observations of Peck *et al.*[7] were correct. Of additional interest in this patient was the fact that when retested after the lapse of a 2-week interval, all tests were negative, indicating the evanescent character of the skin sensitivity, as will be indicated later.

Of the 32 patients in Group 3 with a clinical history of an allergic penicillin reaction 3 had positive skin tests, as shown in Table 3. Of the 3, the data relating to the first one (No. 10) are worthy of more detailed discussion. This patient, who was being treated for tertiary syphilis, had a history of two penicillin reactions. One occurred in May, 1953, and consisted of immediate vomiting and syncope followed the next day by generalized urticaria persisting for a week. Despite this, she was given 1,200,000 units of procaine peni-

UNIVERSITY OF MICHIGAN LIBRARIES

cillin aqueous on July 20, 1953, and again had an immediate reaction with generalized urticaria. Our first tests were done 5½ weeks later and as can be observed in the table, both the scratch and intracutaneous tests were positive in increasing degree according to the concentration used, with negative tests to the vehicles. This was true for both kinds of penicillin, indicating the presence of a specific allergy to penicillin weeks after the appearance of definite evidence of skin sensitiveness to penicillin, the latter began to decrease. This loss of sensitivity became complete within a period of 2 months. As with patient No. 2 these observations likewise suggest that sensitivity to penicillin, at least as indicated by the positive skin test, may be evanescent. This was true to a lesser degree in the second patient in this group (No. 11) who be-

TABLE 2.—DATA ON PATIENTS IN GROUP 2 WITH POSITIVE SKIN TESTS TO PENICILLIN

| | *History of* | | | | | *Skin Test Results* | |
|---|---|---|---|---|---|---|---|
| | | | | | | *Intracutaneous* | |
| *Case No.* | *Allergy* | *Ringworm* | *Type of Penicillin* | *Concentration (Units per cc.) Showing Positive* | *Scratch Test* | *Penicillin* | *Vehicle* |
| 1 | Chronic Dermat. | ..... | Wycillin | 100,000 | Neg. | Sl. | Neg. |
| 2 | ..... | ..... | Bicillin | 100 | | Sl. | |
| | | | | 1,000 | | Sl. Plus | |
| | | | | 10,000 | Neg. | Mkd. | Neg. |
| | | | Wycillin | 100 | | Sl. | |
| | | | | 1,000 | | Sl. | |
| | | | | 10,000 | Neg. | Mod. | |
| 3 | Hay Fever and Asthma | Present | Bicillin | 10,000 | Neg. | Sl. Plus | Neg. |
| | | | Wycillin | 10,000 | Neg. | Sl. Plus | Neg. |
| 4 | Positive Family History | ..... | Bicillin | 1,000 | | Sl. Plus | |
| | | | | 10,000 | | Sl. Plus | Neg. |
| | | | Wycillin | 10,000 | Neg. | Sl. Plus | Neg. |
| 5 | Positive Family History | Present | Bicillin | 100,000 | Neg. | Sl. | Neg. |
| 6 | ..... | ..... | Bicillin | 100,000 | Neg. | Doubtful | Neg. |
| 7 | ..... | ..... | Bicillin | 300,000 | Neg. | Sl. | Sl. |
| 8 | ..... | ..... | Wycillin | 100,000 | Neg. | Sl. | Sl. |
| 9 | ..... | ..... | Wycillin | 10,000 | | Sl. | Sl. |
| | | | | 100,000 | Neg. | Sl. | |

rather than to any of the ingredients. The remarkable features in this patient are the results of the subsequent repeat tests. Thus, when tested in exactly the same way 17 days later, September 14, 1953, a slight but definite diminution in the degree of reaction was observed both with the scratch and intracutaneous methods. But when the tests were repeated on November 9, 1953, after an interval of about 2 months, all the tests were completely negative. Apparently, within 2 to 3 cause of expediency could only be tested intracutaneously. When tested for the first time 19 days after the occurrence of the reaction, he had a positive test to Wycillin in a concentration of 100,000 units per cc. with a negative test to the vehicle. But when retested 4 weeks later, there was a reduction in the degree of reaction, the test now being only moderately positive. Since the patient left the hospital unexpectedly, we unfortunately were unable to do either scratch or other comparative

tests or follow-up retests. In the third patient whom we saw only once and who had had two severe reactions to penicillin about 3 years previously, the intracutaneous tests with Bicillin in a concentration of 100,000 units per cc. were positive in slight degree with negative intracutaneous tests to Wycillin up to 100,000 units per cc. and to the vehicle and negative scratch tests to Bicillin and the vehicle. Just why the patient had a positive test only to Bicillin and not to Wycillin is not clear. Since the test was positive in only slight degree to a high concentration, one could assume that the sensitivity to penicillin was mild, perhaps because of the long interval between the reaction and the time of testing.

TABLE 3.—DATA ON PATIENTS IN GROUP 3 WITH POSITIVE SKIN TESTS TO PENICILLIN

| | | | | | *Skin Test Results: Immediate* | | |
|---|---|---|---|---|---|---|---|
| *Case No.* | *Date of Reaction* | *Date of Penicillin Skin Tests* | *Test Material* | *Concentration (Units per cc.)* | *Scratch Test* | *Intracut. Test* | *Patch Test* |
| 10 | May, 1953 | 8/28/53 | Bicillin | 1,000 | Sl. | Sl. Plus | |
| (A.S.) | Immediate | | | 10,000 | Mod. | Mod. | |
| | and | | | 100,000 | Mkd. | Mkd. | |
| Neg. | Generalized | | | 300,000 | Mkd. | .... | Neg. |
| hist. | | | Vehicle | | Neg. | Neg. | |
| for | 7/20/53 | | Wycillin | 1,000 | Sl. | Mod. | |
| allergy | Immediate | | | 10,000 | Sl. Plus | Mod. | |
| and | and | | | 100,000 | Mod. | Mkd. | |
| ringworm | Generalized | | | 300,000 | Mkd. | .... | Neg. |
| | | | Vehicle | | Neg. | Neg. | |
| | | 9/14/53 | Bicillin | 1,000 | Sl. | Sl. Plus | |
| | | | | 10,000 | Sl. Plus | Mod. | |
| | | | | 100,000 | Mod. | Mod. | |
| | | | | 300,000 | Mod. | .... | |
| | | | Vehicle | | Neg. | Neg. | |
| | | | Wycillin | 1,000 | Sl. | Sl. Plus | |
| | | | | 10,000 | Sl. Plus | Mod. | |
| | | | | 100,000 | Mod. | Mod. | |
| | | | | 300,000 | Mod. | .... | |
| | | | Vehicle | | Neg. | Neg. | |
| | | 11/9/53 | Bicillin | 1,000 | Neg. | Neg. | |
| | | | | 10,000 | " | " | |
| | | | | 100,000 | " | " | |
| | | | | 300,000 | " | " | |
| | | | Vehicle | | " | " | |
| | | | Wycillin | 1,000 | Neg. | Neg. | |
| | | | | 10,000 | " | " | |
| | | | | 100,000 | " | " | |
| | | | | 300,000 | " | " | |
| | | | Vehicle | | " | " | |
| 11 | 9/4/53 | 9/23/53 | Wycillin | 100,000 | | Mkd. | |
| Pos. allergy | | | Vehicle | | | Neg. | |
| hist., neg. | | 10/21/53 | Wycillin | 100,000 | | Mod. | |
| ringworm | | | Vehicle | | | Neg. | |
| 12 | 1951 | 7/8/54 | Bicillin | 10,000 | Neg. | Neg. | |
| (W.W.) | | | | 100,000 | " | Sl. | |
| | General | | Wycillin | 10,000 | " | Neg. | |
| Neg. hist. | Edema | | | 100,000 | " | " | |
| | | | Vehicle | | " | " | |

The remaining 29 patients with a history of previous allergic reactions to penicillin all had negative intracutaneous tests even to concentrations of Bicillin and Wycillin up to 300,000 units. Of the 32 patients in this group, 7 were tested within 6 months after the

reaction, 4 from 6 months to a year afterward, 6 from one to 2 years, and 15 more than 2 years afterward. It is interesting to note that in 2 of the 3 patients with positive reactions, the tests were done within a month after the occurrence of the reaction; whereas in the third, with a slight positive test only to Bicillin, the reaction had taken place about 3 years previously.

None of the 32 patients with a history of a reaction had a positive test to the vehicles. Patch tests done on 11 of them, including the 3 with positive skin tests, also were negative. Likewise, no delayed reactions were noted in this group.

As already indicated, control tests were done with the vehicle used for dissolving the penicillin. Of the 629 patients in all 3 groups tested intracutaneously with the vehicle, 16 or 2.5% had positive tests in slight degree; whereas all 76 scratch tests with the vehicle were negative. Although the percentage of positive tests with the vehicle was small, nevertheless the results indicate that the vehicle itself might give a false positive test. It emphasizes the necessity of including a control test with the vehicle whenever skin tests are being done in an effort to detect the existence of allergy to penicillin. This is well illustrated in Cases 7, 8 and 9 in Table 2, all of whom had slight positive tests not only to the penicillin but also to the vehicle and therefore were nonspecific or false positive tests. If the test with the vehicle had been omitted in these instances, the attending physician might have considered that these patients had positive tests to the penicillin and that a specific allergy had existed.

The question might arise in this connection as to whether patients reacting to penicillin might be allergic to the procaine contained in some preparations (in our case Wycillin) rather than to the penicillin itself. We attempted to determine this at the outset of our investigation by testing patients with a 0.5% solution of procaine. However, this was found to be irritating and produced slight positive tests in patients giving negative reactions to the penicillin preparations. It, therefore, was abandoned and only the true vehicle used.

As already indicated, scratch tests were done on only 77 patients in Groups 2 and 3 with a history of previous penicillin administration. They were so uniformly negative in the first series of patients that their performance was discontinued later, except in those patients with a history of previous allergic reactions or in those giving positive intracutaneous tests. None of the scratch tests done on the patients in Group 2 (Table 2) were positive, even though two patients (No. 2 and No. 4) and especially one of these (No. 2) had definite positive intracutaneous tests in the weaker concentrations. Positive scratch tests were obtained in only one patient (No. 1) in Group 3. As already indicated, this emphasizes again the superior sensitiveness of the intracutaneous method.

Patch tests with the pure penicillin solutions in concentrations of 300,000 units per cc. were done on a total of 36 patients, 25 being in Group 2 and 11 in Group 3. All patch tests were negative. Likewise, follow-up inspection at intervals of 24 and 48 hours of all patients having intracutaneous tests failed to reveal any delayed positives.

At the outset of the investigation, some question arose concerning the stability of the penicillin solutions used in testing patients, particularly as to whether they should be prepared daily prior to their use. We tried to answer this by dividing freshly prepared solutions into two parts, allowing one to remain at room temperature and the

other in the refrigerator. It was our intention to test patients with positive reactions with these two solutions and compare the results with that of the freshly prepared solution. Unfortunately, because of the small number of definite positive reactions, we were able to carry out these comparative tests on only two patients (Nos. 10 and 12). In both instances there was no difference between the results of tests with a freshly prepared solution and the two-month-old solution, one of which was refrigerated and the other kept at room temperature. This would seem to indicate that for testing purposes penicillin solutions remain reasonably stable even at room temperatures.

**Discussion.** These studies have shown that out of a total of 629 patients tested, 13 patients had positive skin tests to varying concentrations of penicillin. But, since 3 patients had positive tests in similar degree to the vehicle, only 10 were specific positives. One of these positive tests was obtained in a patient in the control group of 134 patients. It was slight in degree and only to the maximum concentration used in testing (300,000 units per cc.). Whether the presence in this patient of active ringworm infection or of asthma could explain the positive test is questionable. It also is conceivable that the patient unknowingly might have received penicillin previously, although this likewise could apply to other members of the control group.

Excluding the control group, therefore, there were 9 positive tests in a total of 495 patients in Groups 2 and 3 who received penicillin, an incidence of 1.8%. Most of these were slight in degree even with high concentrations of the penicillin solutions. The incidence of positives in those patients with a history of previous allergic reactions (Group 3) seemed appreciably higher (9.4%) than in those without such a history (1.3% of Group 2); but the total number tested in the former group (32) is too small for accurate evaluation compared with the larger number (463) in the nonreacting group. It does suggest, however, that positive skin tests are more likely in patients with a history of a previous allergic reaction to penicillin.

Of great interest also is the relationship of the time interval between the occurrence of the reaction and the performance of the test. Apparently the shorter the interval the more likelihood is there of obtaining a positive test. Thus 2 of the 3 patients in Group 3 with positive tests to penicillin were tested within a relatively short period (2 weeks to 2 months) after the reaction, whereas of the 21 tested more than one year after their reactions, only one was positive. Even if a positive test is obtained, it may be temporary or evanescent. This was emphasized strikingly in patient No. 10 in the reactor group who completely lost a marked degree of skin sensitivity to penicillin within a period of 2 months; also in patient No. 2 in Group 2 who lost her skin sensitivity after an interval of 2 weeks. These experiences verify the similar observations in the literature concerning the temporary nature of the positive skin test. Thus Kern and Wimberley state that it may happen in from 8 to 24 months, but apparently as indicated by our experience it may take place even sooner. Therefore, unless the patient suspected of penicillin allergy is tested within a short period (perhaps a few months) after the occurrence of a reaction, the skin test may be negative. It should be remembered always, as emphasized by others, that although a positive test should be taken as an indication of definite penicillin allergy and that a reaction is more likely to follow a subsequent injection, a negative test does not exclude this possibility, especially

if the patient is asthmatic and had previously received penicillin.

Finally, the results of these investigations seem to answer more definitely the question as to the type of test to be used for the detection of penicillin sensitivity. The most satisfactory tests for that purpose are the scratch and intracutaneous tests, since both give immediate urticarial reactions that can be read within a short time after their performance. No reliance should be placed upon the delayed type of test which has to be read in 24 to 48 hours, since this is of no use in the immediate or anaphylactic type of penicillin allergy. Patch tests also should not be used except in patients with a contact type of allergic dermatitis when penicillin is suspected to be the contactant agent.

The outstanding advantage of the intracutaneous technique of testing over the scratch method is its superior sensitiveness and, therefore, its greater likelihood of being positive. This was emphasized in most of our patients, especially in patients Nos. 2 and 11, both of whom had definite positive intracutaneous tests with negative scratch tests to penicillin even in higher concentrations. It certainly is the test method of choice whenever one is trying to detect the presence of allergy to penicillin. The amount to be used is that employed regularly in the intracutaneous test with routine allergens, namely 0.02 cc. As to the concentration to be employed, we would recommend without hesitation testing with penicillin in a concentration of 10,000 units per cc., were it not for one disturbing report in the literature. This was the mention by Mayer *et al.*[6] in his report, in 1953, of a severe constitutional reaction having followed the intracutaneous injection of 0.01 cc. of a solution containing 1,000 units per cc. But closer inspection of this report revealed that this test was done while the patient was in the throes of his acute allergic reaction and thus explains the constitutional reaction which followed the test. Since patients about to receive penicillin usually are free of any reaction, it is unlikely that they will be as sensitive as the above patient. Despite this report, therefore, and from our experience with intracutaneous testing in other allergic conditions, we still believe that intracutaneous tests with 0.02 cc. of penicillin in a concentration of 10,000 units per cc. can be used with safety as a means of detecting penicillin allergy. This may be preceded, if so desired, by a preliminary scratch test. But if this is negative, the intracutaneous test still must be done before penicillin allergy can be excluded. Considering how difficult it is to get physicians even to think of testing patients prior to penicillin administration, it is doubtful whether many would be willing to do a scratch test first and then an intracutaneous one. From a practical standpoint, therefore, the intracutaneous method is the method of choice. It should be done on all patients in whom the history suggests the possible presence of penicillin allergy. As already indicated, a control test with the vehicle should always be done at the same time to exclude the possible occurrence of a false positive test.

**Summary and Conclusions.** 1. Of 495 patients receiving penicillin, specific positive tests occurred in 9 or 1.8% with the incidence apparently higher in those with a history of allergic reaction to the penicillin.

2. A positive skin test to penicillin, indicative of the presence of the anaphylactic type of allergy may be highly evanescent and disappear within a short time, even within 2 or 3 months. Therefore, the shorter the interval between the occurrence of the reaction and the time of testing, the greater the

likelihood of obtaining a positive skin test. *A negative skin test, however, does not exclude penicillin allergy and the possibility of a reaction to a subsequent administration, especially if the patient is allergic (for example, asthmatic) and had been given penicillin previously.*

3. The most satisfactory skin test method for the detection of penicillin allergy is the intracutaneous injection of 0.02 cc. of a concentration of penicillin of 10,000 units per cc. This may be preceded by a scratch test where exquisite sensitiveness is suspected. In either instance, a control test with the penicillin diluent or vehicle should always be done at the same time to exclude a possible false positive test. No reliance can be placed on delayed positive skin tests. Patch tests are useful only in the contact form of allergic dermatitis to penicillin but not in the anaphylactic form.

## REFERENCES


1. **Feinberg, S. M., Feinberg, A. R.,** and **Moran, C. F.:** J. Am. Med. Assn., **152**, 114, 1953.
2. **Hopkins, J. G.,** and **Lawrence, H.:** J. Allergy, **18**, 251, 1947.
3. **Kadison, E. R., Ishihara, S. J.,** and **Waters, T.:** Am. Pract. & Dig. Treat., **2**, 411, 1951.
4. **Kern, R. A.,** and **Wimberley, N. A., Jr.:** Am. J. Med. Sci., **226**, 357, 1953.
5. **Kolodny, M. H.,** and **Denhoff, E.:** J. Am. Med. Assn., **130**, 1058, 1946.
6. **Mayer, P. S., Mosko, M. M., Schutz, P. S., Ostorma, F. A., Stein, L. H.,** and **Baker, L. A.:** Ibid., **151**, 351, 1953.
7. **Peck, S. M., Siegal, I., Glick, A. W., Kurtin, A.,** and **Bergamini, R.:** Ibid., **138**, 631, 1948.
8. **Risman, G.,** and **Boger, W. P.:** J. Allergy, **21**, 425, 1950.


## SUMMARIO E CONCLUSIONES IN INTERLINGUA

### Evalutation del Methodos de Essayage Dermatic Usate in le Diagnose de Allergia a Penicillina


A causa del manco de standardisation in le methodos de essayage usate usque nunc in le diagnose de allergias a penicillina, nos ha interprendite un investigation comparative del valor de ille methodos. Le resultatos obtenite forma le base del presente reporto.

1. Inter 495 patientes recipiente penicillina, 9 (o 1,8 pro cento) habeva essayos specificamente positive. Le casos positive esseva apparentemente le plus concentrate inter le patientes con un historia de reactiones allergic a penicillina.

2. Un positive essayo dermatic a penicillina, indicante le presentia del typo anaphylactic de allergia, pote esser multo evanescente; illo pote disparer intra un breve tempore, mesmo intra 2 o 3 menses. Ergo, le plus breve le intervallo inter le occurrentia del reaction e le tempore del essayo, le plus grande le probabilitate de obtener un resultato positive. *Tamen, un essayo dermatic negative non prova le absentia de allergia a penicillina e non exclude le possibilitate de un reaction a un administration subsequente, specialmente si le patiente es allergic (per exemplo asthmatic) e si ille ha previemente recipite penicillina.*

3. Le plus satisfacente methodo de essayage dermatic pro deteger allergias a penicillina es le injection intracutanee de 0,02 $cm^3$ de penicillina in un concentration de 10.000 unitates per $cm^3$. Isto pote esser precedite per un essayo a grattage in casos in que un sensibilitate exquisite es a suspicer. Con ambe iste procedimentos un simultanee essayo de controlo debe esser executate con le diluente per se pro excluder le possibilitate de resultatos falsemente positive. Essayos dermatic a retardate effectos positive non es de valor probatori, e essayos a contacto es utile solmente in le forma contactile de dermatitis penicillino-allergic sed non in le forma anaphylactic.

# RELATIONSHIP OF MORTALITY FROM MYOCARDIAL INFARCTION TO PATHOLOGIC FINDINGS AND AGE

By Thomas B. Smart, M.D.
CLINICAL ASSOCIATE IN MEDICINE

AND

Robert A. Bruce, M.D.
ASSOCIATE PROFESSOR OF MEDICINE

(From the Department of Medicine, University of Washington, Seattle, Washington)

The mortality from myocardial infarction varies widely from good risk to poor risk patients[1,4,11]. Statistics have been reported indicating mortality experience as low as 6%[3] and as high as 78%[2]. Recently, Schnur has proposed a method of predicting mortality from myocardial infarction which is based upon clinical manifestations generally considered to bear a poor prognosis. A numerical value is assigned to each clinical finding or complication known to unfavorably influence prognosis in myocardial infarction (Table 1). The total score derived from those features known to be present when the patient is admitted for hospital care is designated the Pathologic Index Rating. This index has been useful in accounting for variations in mortality experience in different hospital patients and for different years in the same hospital[6,7,9]. In addition, it has been of value in appraising therapeutic regimens, such as anticoagulants, employed for myocardial infarction[6].

TABLE 1.—NUMERICAL VALUES FOR THE CLINICAL FEATURES USED TO COMPUTE PATHOLOGIC INDEX RATINGS

| | | | |
|---|---|---|---|
| Shock | 40 | Associated Diseases | 10–25 |
| Congestive heart failure | 20–25 | Diabetes | 10–25 |
| Arrhythmias | | Uremia | 10–25 |
| Occasional PVS | 10 | Urinary infection | 10 |
| Frequent PVS | 15 | Emphysema | 10 |
| Auricular tachycardia | 15 | Cerebral thrombosis | 10–25 |
| Auricular fibrillation | 25 | History of heart or vascular disease | 10–30 |
| Auricular flutter | 30 | Hypertension | 10 |
| Ventricular tachycardia | 40 | Cardiac enlargement | 15 |
| Gallop | 15 | Angina | 10–30 |
| | | Cong. heart failure | 20–30 |
| | | Prev. cor. occl. | 20–30 |

*Schnur, Ann. Int. Med., Nov., 1953.

During a recent 30-month period, the over-all mortality from myocardial infarction was 74% at the King County Hospital, Seattle, Washington. If mortality from myocardial infarction varies from good risk to poor risk patients, the high mortality at this institution may be a reflection of a predominantly large number of poor risk patients, and not necessarily a reflection of inade-

quate treatment. For clarification of this question, it was important to evaluate the mortality in terms of the Pathologic Index, to determine if there were any significant deviations from the reported findings of Schnur.

**Material and Methods.** The clinical records of patients discharged from the King County Hospital between January 1, 1951, and July 1, 1953, with a diagnosis of myocardial infarction were reviewed. Only those records that presented unequivocal clinical findings, classical electrocardiographic changes or confirmatory necropsy evidence or any combination of these were included. Sixty-nine per cent of the fatal cases came to necropsy.

The Pathologic Index was determined from the recorded information on the chart at the time of admission. Schnur's scoring was used, and certain variables that could be weighted were assigned values within the indicated range, according to the apparent severity of the particular manifestation.

**Results.** There were 160 patients with acute myocardial infarction dur-

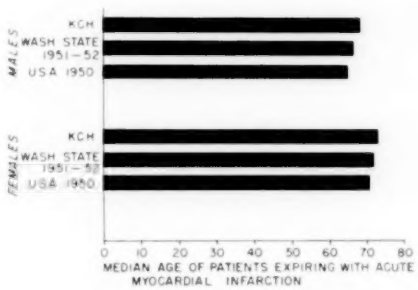


Fig. 1.—Comparison of median age of patients with fatal myocardial infarction in the King County Hospital, State of Washington, and U.S.A.

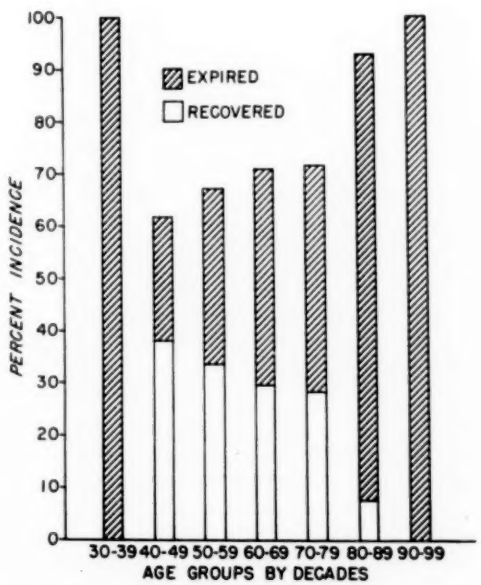


Fig. 2.—The distribution of myocardial infarction according to age, and relationship of mortality to age.

ing this 30-month period. Of these, 98 were males ranging in age from 33 to 89 years, with a median age of 67.4 years; 62 were females ranging in age from 44 to 93 years, with a median age of 70.5. The median age for each sex, as shown in Fig. 1, exceeded the median ages of patients reported for Washington State in 1951–1952 and for the United States in 1950[10].

The uncorrected mortality for the entire group of 160 patients was 74.0%. It is important to note, however, that 40 patients died within 24 hours of admission, making a corrected mortality of 49.3% for those patients surviving longer than one day. The distribution of patients in relation to age, and the relationship of age to fatality is shown in Fig. 2.

In accord with Schnur's report[9], mean age apparently was not an important prognostic factor in male patients under 75 years of age. An average age of male survivors of 67.8 years compared favorably with an average age of 68.3 years for those who expired. The average age of surviving females of 64.9 years contrasted with an average age of 72.7 years for the fatal cases.

The apparent discrepancies in mortality in relation to age can be clarified by analyzing the data in terms of the Pathologic Index (Table 2). Seven patients with a low index of 0 to 19 had a mortality rate of 28.6% despite an average age of 69.5 years. Conversely, 29 patients with high indices of 80 and over had a case fatality rate of 96.6%, with an average age of 68.2 years. Intermediate groups with Pathologic Indices ranging from 40 to 79 had case fatality rates of 72.7 to 86.5%. These results tend to confirm the findings reported by Schnur[9], that the Pathologic Index Rating is a much more important prognostic factor than the patient's age.

The distribution of patients according to the Pathologic Index Rating is shown in Fig. 3, and compared with the material reported by Schnur. The relationship of the Pathologic Index Rating to mortality is shown in Fig. 4. Only those patients surviving longer than 24 hours are included in this comparison, in order that the material would be selected in a manner comparable to that reported by Schnur. Despite considerable differences in distribution of patients within these two groups, the relationship between Pathologic Index and mortality was virtually identical for both groups (Fig. 4). The only exception was in regard to 3 patients with a low index of 0 to 19. Undoubtedly the sample was not large enough to permit adequate evaluation in this range.

TABLE 2.—DISTRIBUTION OF PATIENTS WITH ACUTE MYOCARDIAL INFARCTION ACCORDING TO PATHOLOGIC INDEX

| *Pathologic Index* | *Number of Patients* | *Average Age (years)* | *Expired Number* | *Patients %* |
|---|---|---|---|---|
| 0–19 | 7 | 69.5 | 2 | 28.6 |
| 20–39 | 20 | 66.9 | 4 | 20.0 |
| 40–59 | 52 | 69.8 | 38 | 72.7 |
| 60–79 | 52 | 70.3 | 45 | 86.5 |
| 80 and over | 29 | 68.2 | 28 | 96.6 |
| | 160 | | 117 | 73.3 |

**Discussion.** Although the distribution of case material presented here is quite different from that previously reported by Schnur, the relationship of the Path-

ologic Index to mortality is strikingly similar in the two studies. That is to say, the severity of illness, in terms of pathologic complications at the time of admission, is more closely related to mortality from myocardial infarction than other factors, such as age. Nevertheless, it is true that older patients tend in most instances to have higher Pathologic Indices.

In view of these relationships, any evaluation of therapeutic regimens (such as anticoagulants) for myocardial infarction should include an analysis of the Pathologic Index of both treated and control groups before differences in mortality experience can reliably be attributed to therapy.

**Summary and Conclusions.** 1. The clinical records of 160 patients with

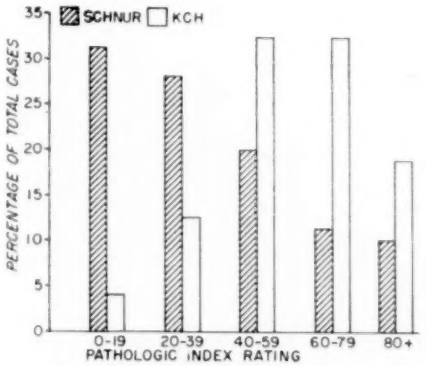


Fig. 3.—Comparison of the distribution of patients in this series with those reported by Schnur, according to Pathologic Index Rating.

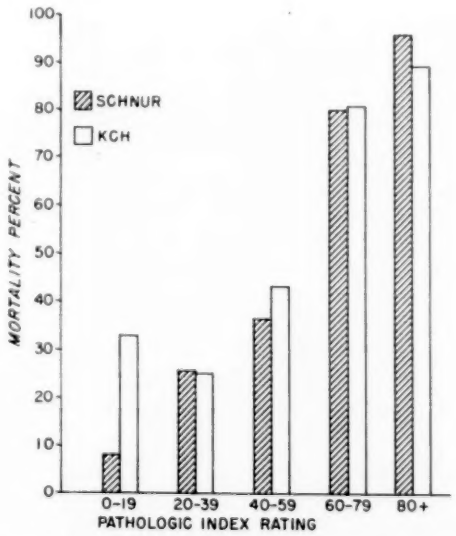


Fig. 4.—The relationship between Pathologic Index Ratings and mortality.

myocardial infarction were surveyed to evaluate pathologic findings in relation to mortality. Necropsy records were available on 69% of 117 fatal cases. The Pathologic Index Rating advocated by Schnur was determined for each patient on the basis of admission findings.

2. Although the distribution of patients according to Pathologic Index Rating varied widely from those reported by Schnur, the results of classifying mortality according to Pathologic Indices were almost identical.

3. It is concluded that the severity of pathologic complications on admission are more important than age, although older patients usually have higher Pathologic Indices.

4. The Pathologic Index Rating appears to be a valid index of prognosis and should be utilized in evaluating therapeutic regimens for myocardial infarction with respect to mortality experience.

## REFERENCES

1. **Cole, D. R., Singran, E. B.,** and **Katz, L. N.:** Circulation, **9,** 321, 1954.
2. **Newman, M.:** Lancet, **2,** 409, 1946.
3. **Russek, H. I.,** and **Zohman, B. L.:** Am. J. Med. Sci., **228,** 133, 1954.
4. **Russek, H. I., Zohman, B. L., Doerner, A. A., Russek, A. S.,** and **White, L. G.:** J. Am. Med. Assn., **147,** 1731, 1951.
5. Iidem: Circulation, **5,** 707, 1952.
6. **Schnur, S.:** Ibid., **7,** 855, 1953.
7. Idem: Ann. Int. Med., **39,** 1014, 1953.
8. Idem: Ibid., **39,** 1018, 1953.
9. Idem: Ibid., **41,** 294, 1954.
10. Washington State Department of Health. Personal communication, 1954.
11. **Wooton, R. L.,** and **Kyser, F. A.:** Ann. Int. Med., **38,** 247, 1953.

## SUMMARIO E CONCLUSIONES IN INTERLINGUA

### Relation del Mortalitate ab Infarcimento Myocardiac con Constatationes Pathologic e con le Etate del Patientes

1. Esseva examinate le protocollos clinic de 160 patientes con infarcimento myocardiac pro evalutar le constatationes pathologic in relation al mortalitate. Protocollos necroptic esseva disponibile pro 69 pro cento del 117 casos mortal. Le Indice Pathologic, secundo le recommendationes de Schnur, esseva determinate pro cata patiente super le base del constatationes al tempore del admission al hospital.

2. Ben que in nostre studio le distribution del patientes secundo lor Indices Pathologic differeva considerabilemente ab le distribution del patientes in le reporto de Schnur, le resultatos del classification del mortalitate secundo le Indices Pathologic esseva quasi identic in le duo casos.

3. Nos conclude que le severitate del complicationes pathologic al tempore del admission del patiente es plus importante que su etate, sed il es ver que le patientes de etates plus avantiate ha generalmente plus alte Indices Pathologic.

4. Le Indice Pathologic pare representar un valide criterio prognostic. Illo deberea esser prendite in consideration in omne evalutation de un therapia pro infarcimento myocardiac in relation al grado de mortalitate que es obtenite per illo.

# THE SEVERITY OF AORTIC ARTERIOSCLEROSIS IN CERTAIN DISEASES: A NECROPSY STUDY

By Donald L. Creed, M.D.
TEACHING FELLOW IN PATHOLOGY

William F. Baird, M.D.
TEACHING FELLOW IN PATHOLOGY

AND

Edwin R. Fisher, M.D.
ASSOCIATE PROFESSOR OF PATHOLOGY

(From the Departments of Pathology of the University of Pittsburgh, School of Medicine and Veterans Administration Hospital, Pittsburgh, Pennsylvania)

Although the actual mechanisms involved in the development of human arteriosclerosis have not been clearly elucidated, the possibility that certain diseases may influence its evolution is worthy of consideration. Experimental and other studies have indicated that arteriosclerosis may be the result of discontinuous stimuli or repeated insults to the vascular system throughout the course of an individual's life[3,11]. It is also appreciated that arteriosclerosis may be labile and not necessarily associated with old age. Such contentions suggest that certain disease processes may influence the development of arteriosclerosis.

It is well recognized that syphilitic aortitis, diabetes mellitus, xanthomatosis, hypothyroidism and so-called lipoid nephrosis, as well as hypertension are often accompanied by severe arteriosclerosis. Hall, Olsen and Davis[10], on the other hand, observed a decreased incidence in patients with Laennec's cirrhosis. Aside from these observations there has been little exploration into the association of other diseases with arteriosclerosis.

It is the purpose of this investigation to disclose evidence that arteriosclerosis is significantly influenced by other diseases than those previously noted. The possible mechanisms underlying these relationships shall be discussed.

**Material and Methods.** This study consisted of an evaluation of the severity of aortic arteriosclerosis encountered in 1,223 necropsies performed on males at the Veterans Administration Hospital at Aspinwall, Pa., during the 7-year period from 1946 to 1952 inclusively. One thousand fifty-six of the aortas were evaluated from the details of necropsy protocols described by others, and 167 were examined and evaluated at the time of necropsy by at least one of us. The degree of aortic arteriosclerosis was graded according to the following macroscopic features: Grade 0, no visible arteriosclerosis; Grade I, superficial fatty-streaking of the intima; Grade II, fibrous intimal plaques; Grade III, calcification or ulceration, or both, of the abdominal aorta with or without the lesions of Grades I and II; Grade IV, similar to Grade III except that ulceration or calcification, or both, were present in both the abdominal and thoracic portions of the aorta. These grades were extrapolated to a percentage value. Grades 0–I represented 0 to 25%, Grades I–II, 26 to 50%; Grades II–III, 51 to 75% and Grades III to IV, 76 to 100%.

This expression of the severity of aortic arteriosclerosis was tabulated in each instance according to the major disease accounting for the patient's death as disclosed at necropsy. Although various diseases were encountered, only those which appeared to be related to a statistically significant increase or decrease of aortic arteriosclerosis are to be considered in the results.

The major diseases were also categorized into age groups having a 5-year span. Any group with less than 5 samples was discarded. The degree of arteriosclerosis, as extrapolated above, was also recorded in its appropriate age and disease group. The mean of the percentage of arteriosclerosis was then determined. The value obtained represented the mean percent of the degree of arteriosclerosis of all cases associated with a particular disease in a specified age group. Probability values were determined on the difference between the means of the control group and the disease or condition evaluated. Yates' correction for continuity for chi square with Fisher's adjustment for normalization was utilized[8].

A control curve eliminating the factor of hypertension was obtained in a similar fashion from patients whose blood pressure was recorded in their clinical records as not being greater than 170 mm. Hg systolic and 100 mm. Hg diastolic. Also aortas from patients whose major disease was diabetes, bronchogenic carcinoma, malignant lymphoma including leukemia, syphilitic aortitis or who demonstrated jaundice (obvious gross jaundice or an icterus index of greater than 14) were excluded, since patients with these diseases and clinical manifestation revealed statistically significant differences of arteriosclerosis.

The effect of weight loss was evaluated in relationship to the severity of aortic arteriosclerosis. This was considered as rapid when there was the loss of 20 or more pounds within 6 months prior to death.

The possible effect of irradiation on aortic arteriosclerosis was analyzed from the records of patients with bronchogenic carcinoma who received Roentgen therapy. Although the total dose varied somewhat in each patient, only those receiving approximately 5000 r were included.

**Results.** Aortic arteriosclerosis was more severe (of higher grade) in patients succumbing to hypertension or bronchogenic carcinoma. These differed from the control group with a "p" value of less than 0.01. The only statistically valid age range for this change in patients with bronchogenic carcinoma was 41 to 65 years, while that for the hypertensive group was 51 to 65 years. The curves of arteriosclerosis in these diseases, as depicted in Fig. 1, are roughly parallel. No significant difference could be discerned in the degree of arteriosclerosis encountered in patients with bronchogenic carcinoma who received Roentgen therapy from those in whom this therapeutic measure was not employed (Fig. 2). Although the results indicated that rapid weight loss, as defined previously, was accompanied by an increased severity of arteriosclerosis this did not appear to be a significant factor in the degree of change noted in patients with bronchogenic carcinoma. Other malignant neoplasms such as carcinoma of the head of the pancreas and colon were also associated with rapid weight loss but without a statistically significant increased severity of arteriosclerosis.

On the other hand, the aortas of patients with either malignant lymphoma or leukemia revealed a statistically significant decreased severity of arteriosclerosis in the range of 51 to 60 years (Fig. 1). A similar decrease of arteriosclerosis, particularly between the ages 51 and 55, was encountered in patients with Laennec's cirrhosis (Fig. 3). Other examples of liver diseases were too few for statistical evaluation.

Chronic weight loss or no weight loss was not accompanied by the degree of arteriosclerosis that was encountered in patients with rapid loss of weight. This differed from the control group with a "p" value of less than 0.05 (Fig. 4).

There was no significant difference between the results obtained by utilizing previous necropsy reports and those aortas graded by us at the time of necropsy.

**Discussion.** The results of this study reaffirm the observations of an increased severity of arteriosclerosis in patients with hypertension. Evidence is presented that bronchogenic carcinoma is also associated with such an increase. This appears to be directly associated with

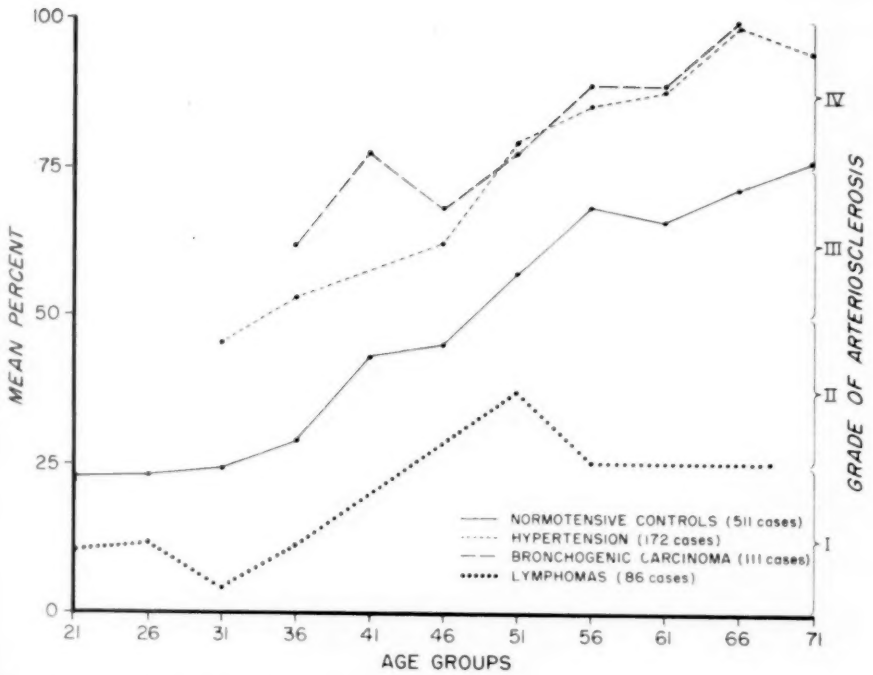


Fig. 1.—The severity of aortic arteriosclerosis in patients with hypertension, bronchogenic carcinoma and lymphomas as compared to normotensive controls.

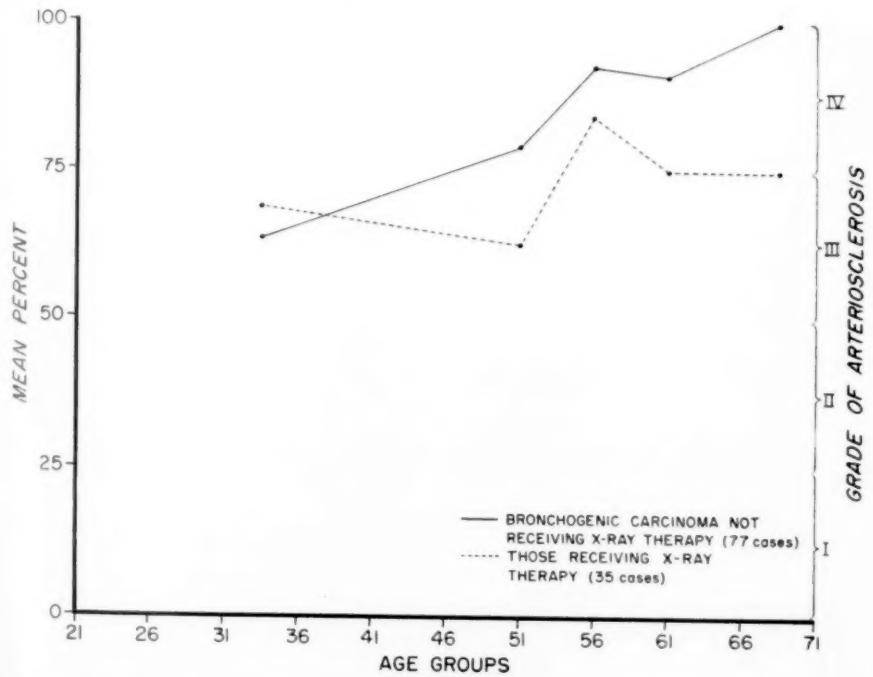


Fig. 2.—Comparison of severity of aortic arteriosclerosis in patients with bronchogenic carcinoma with and without Roentgen therapy.

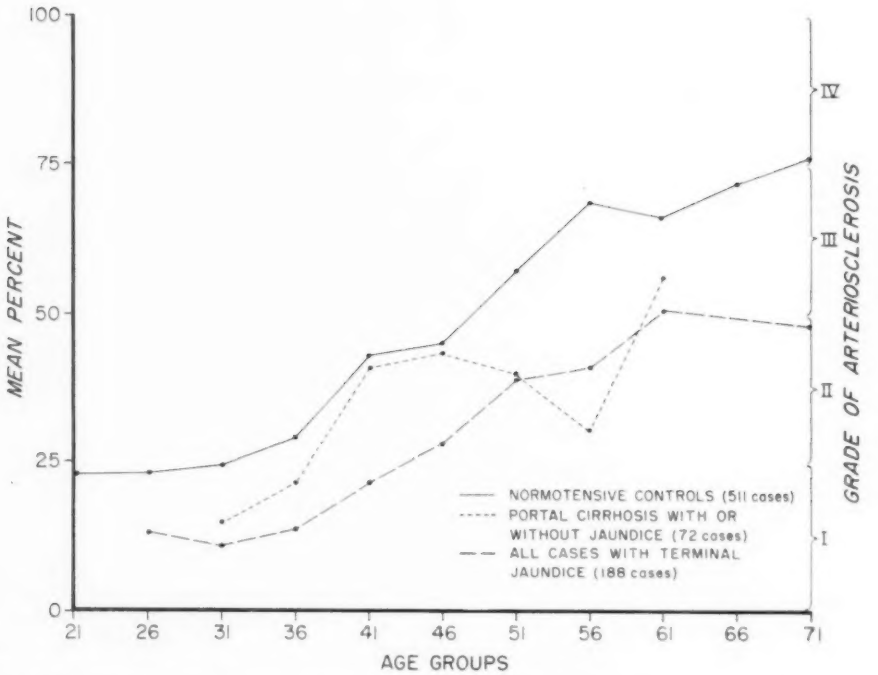


Fig. 3.—Severity of aortic arteriosclerosis in patients with hepatic cirrhosis (with or without jaundice) and all patients with terminal jaundice compared with control group.

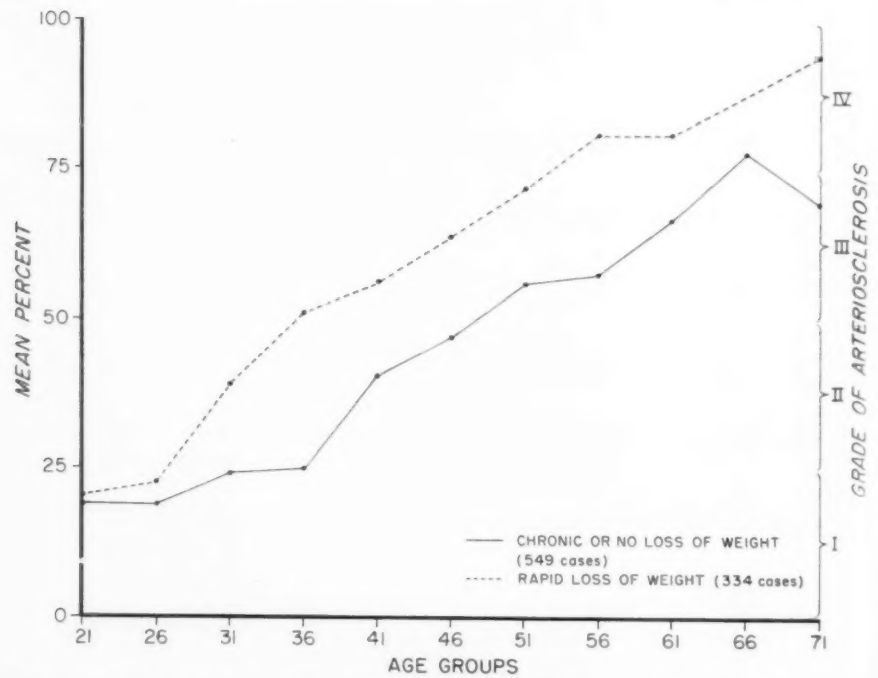


Fig. 4.—Comparison of severity of aortic arteriosclerosis in patients with rapid and chronic weight loss.

this type of malignant tumor, rather than the presence or absence of hypertension or old age in these patients. In addition, this relationship cannot be explained on the basis of rapid weight loss, for such an alteration in nutrition was found in other neoplastic diseases not associated with comparable degrees of arteriosclerosis. Whether the smoking factor appears to be as important in the development of arteriosclerosis as purported for bronchogenic carcinoma cannot be affirmed or refuted, especially since the exact role of tobacco in the pathogenesis of bronchogenic carcinoma has not been conclusively established. The high incidence of adrenal metastases (45% in this series) in bronchogenic carcinoma might suggest the possible effects of adrenal destruction in the development of human arteriosclerosis. However, similar degrees of arteriosclerosis were noted in patients without adrenal metastases. Adrenal destruction as the result of metastases from other primary tumors not associated with severe arteriosclerosis was not infrequently observed.

Numerous studies have attempted to correlate obesity and malnutrition with arteriosclerosis. Unfortunately, many have neglected to consider the rapidity of nutritional change as a factor in their correlations. However, the results of this study have indicated that the duration of weight loss is a significant factor. Wilens[15] found obesity to be associated with arteriosclerosis of the coronary arteries almost twice as frequently as malnutrition from a study of 1,252 necropsies. Faber and Lund[7] have attributed the increase of arteriosclerosis in obesity to its great relationship to diabetes and hypertension rather than the obesity *per se*. On the other hand, Garn and associates[9] failed to find an increased severity of obesity in men under 40 years of age with myocardial infarction. The decreased incidence of arteriosclerosis in countries with a low dietary fat intake imposed by wartime restrictions might be considered as a chronic rather than rapid change in nutrition. This study suggests that rapid loss of weight and possible rapid overloading of the blood plasma with lipid from fat stores may be significant in the development of arteriosclerosis.

As previously observed, the results of this study indicate a diminution in the severity of arteriosclerosis in patients with Laennec's cirrhosis. Several possible mechanisms for such a finding are worthy of comment. It has been claimed that the stability of the lipoprotein fraction of the serum may depend on the type of protein supplied by the liver[4]. It is this factor which has recently been recognized by many investigators to be of greater significance in arteriosclerosis than the actual degree of cholesterol alteration in the serum fraction[1,5,12]. It is well appreciated that in cirrhosis protein aberrations are encountered. That these may lead to more stable lipoprotein complexes is not unduly presumptuous. Another feature of cirrhosis, namely, inadequate inactivation of estrogen, may be an important factor in the inhibition of arteriosclerosis encountered in this disease[6,14]. Barr[3] has demonstrated a marked difference in the serum alpha and beta lipoprotein fractions of sera of young women as compared to that of women and men between the ages of 45 and 60. Recently[2] he has shown that the administration of estrogen alters the serum lipoprotein pattern in males, producing patterns similar to that noted in young women with minimal arteriosclerosis. In addition, he has observed that the beta lipoproteins which were increased in patients who have survived myocardial infarction were altered by estro-

gen, so that the pattern was similar to that noted in healthy young women. Such evidence indicates a heparin-like clearing action of estrogen on serum lipoproteins. The increased incidence of arteriosclerosis in bilaterally oöphorectomized women also supports this contention[16].

The effect of jaundice *per se* on arteriosclerosis is worthy of comment. It has been reported that some hepatic diseases associated with jaundice are accompanied by an elevation of serum phospholipids[13] which is an important factor in the stabilization of serum lipid emulsions. Some investigations have indicated that altered cholesterol-phospholipid ratios result in decreased stability of lipoproteins as noted in arteriosclerosis[1,5,12].

No explanation is apparent for the definitely decreased severity of arteriosclerosis in patients with malignant lymphomas including leukemia. However, the marked liver involvement frequently noted in the patients with these diseases in this series may offer some explanation for such an effect.

**Summary and Conclusions.** 1. Statistically significant differences in the severity of arteriosclerosis of the aorta have been observed in a necropsy study of the aortas of 1,223 male patients with hypertension, bronchogenic carcinoma, Laennec's cirrhosis and malignant lymphomas as well as rapid weight loss.

2. Patients with hypertension and bronchogenic carcinoma have been found to have a greater degree of arteriosclerosis than control patients.

3. On the other hand, patients with Laennec's cirrhosis and those with malignant lymphoma tend to have a decreased severity of this degenerative process.

4. The mechanism accounting for an increased severity of arteriosclerosis in patients with bronchogenic carcinoma is not apparent. Explanation for a decreased severity of arteriosclerosis in patients with hepatic cirrhosis might well reside in the clearing action of estrogen upon serum lipoproteins. Failure of estrogen inactivation is well recognized in this disease. In addition, the presence of jaundice which is associated with increased serum phospholipids, an important factor in the stabilization of serum lipid emulsions, may also play a role. The frequent hepatic involvement observed in patients succumbing to malignant lymphomas and leukemia may account for the decreased severity of arteriosclerosis in patients with these diseases. In addition, it has been noted that a prolonged poor nutritional state, which many of these patients exhibit, is associated with a decreased severity of arteriosclerosis.

## REFERENCES

1. **Ahrens, E. H., Jr.,** and **Kunkle, H. G.:** J. Exper. Med., **90,** 409, 1949.
2. **Barr, D. P.:** J. Chronic Dis., **1,** 63, 1955.
3. **Barr, D. P., Russ, E. M.,** and **Eder, H. A.:** Circulation, **6,** 455, 1952.
4. **Byers, S. O., Friedman, M.,** and **Rosenman, R. H.:** Metabolism, **1,** 479, 1952.
5. **Duff, G. L.,** and **Payne, T. P. B.:** J. Exper. Med., **92,** 299, 1950.
6. **Edmondson, H. A., Glass, S. J.,** and **Soll, S. N.:** Proc. Soc. Exper. Biol. & Med., **42,** 97, 1939.
7. **Faber, M.,** and **Lund, F.:** A.M.A. Arch. Path., **48,** 351, 1949.
8. **Fisher, R. A.:** Statistical Methods for Research Workers. Edinburgh: Oliver & Boyd, 1950.
9. **Garn, S. M., Gertler, M. M., Levine, S. A.,** and **White, P. D.:** Ann. Int. Med., **34,** 1416, 1951.

10. **Hall, E. M., Olsen, A. Y.,** and **Davis, F. E.:** Am. J. Path., **29,** 993, 1953.
11. **McGill, H. C., Peck, G.,** and **Holman, R. L.:** Circulation, **6,** 466, 1952.
12. **Morrison, L. M., Gonzalez, P.,** and **Wolfson, E.:** Circulation, **2,** 472, 1950.
13. **Petersen, V. P.:** Acta med. scandinav., **144,** 333, 1953.
14. **Schiller, J.,** and **Pincus, G.:** Endocrinology, **34,** 203, 1944.
15. **Wilens, S. L.:** A.M.A. Arch. Int. Med., **79,** 129, 1947.
16. **Wuest, J. H., Dry, T. J.,** and **Edwards, J. E.:** Circulation, **6,** 461, 1952.

## SUMMARIO E CONCLUSIONES IN INTERLINGUA

### Le Severitate de Arteriosclerosis Aortic in Certe Morbos: Un Studio Necroptic

1. In un studio necroptic, differentias de signification statistic esseva observate in le severitate del arteriosclerosis aortic de 1223 patientes mascule con hypertension, carcinoma bronchogenic, cirrhosis de Laennec, lymphomas maligne, e etiam con rapide decrescentia del peso corporee.

2. Il esseva constatate que patientes con hypertension e con carcinoma bronchogenic habeva plus alte grados de arteriosclerosis que patientes de controlo.

3. Del altere latere, in patientes con cirrhosis de Laennec e in patientes con lymphoma maligne le processo degenerative del arteriosclerosis tendeva a manifestar se con un severitate minus pronunciate.

4. Le mechanismo responsabile pro le plus sever grado de arteriosclerosis in patientes con carcinoma bronchogenic non es clar. Un explication del reducite severitate del arteriosclerosis in patientes con cirrhosis hepatic es possibilemente a trovar in le effecto clarificante de estrogeno super le lipoproteinas del sero. Le inadequate inactivation de estrogeno in iste morbo es ben cognoscite. In plus, il es possibile ascriber un certe importantia in le situation al existentia de ictero que es associate con un augmento del phospholipidos del sero. Istos es un factor importante in le stabilisation de emulsiones lipide del sero. Le frequente involvimento hepatic que se observa in patientes qui ha succumbite a lymphomas maligne e a leucemia es possibilemente un explication del reducite severitate de arteriosclerosis in ille casos. In plus, il ha essite constatate que le prolongate stato inferior del nutrition que characterisava multes del patientes in nostre serie esseva associate con un reducite severitate del arteriosclerosis.

# EFFECTS OF POTASSIUM AND CORTISONE ON MORBIDITY AND HYPONATREMIA FOLLOWING MITRAL VALVE SURGERY*

By ROBERT A. BRUCE, M.D.
ASSOCIATE PROFESSOR OF MEDICINE

AND

K. ALVIN MERENDINO, M.D.
ASSOCIATE PROFESSOR OF SURGERY

WITH THE TECHNICAL ASSISTANCE OF
B. LIPSHAY

(From the Departments of Medicine and Surgery, University of Washington, Seattle, Washington)

*These studies have been supported in part by Grant-in-Aid H-1468 from the National Heart Institute of the National Institutes of Health, Public Health Service.

OUR initial experiences with mitral valve surgery in 1952 revealed an unexpected morbidity during the first week after operation. Investigation of the metabolic responses to cardiac surgery demonstrated hyponatremia in several patients. The effects of altering the conventional regimen of postoperative fluid management to determine the role of water and sodium in this early morbidity have been reported elsewhere[1].

Hyponatremia, defined as serum sodium concentration below 127 mEq./L., occurred in 4 out of 12 patients who were permitted an "unrestricted" intake of water averaging 2.6 L. *per diem*. Intravenous saline corrected "symptomatic" hyponatremia in 2 patients who may have been depleted of sodium preoperatively by prolonged medical treatment. This treatment did not cause pulmonary congestion. The prophylactic use of limited amounts of sodium, averaging 60 mEq. *per diem*, not only failed to prevent hyponatremia in 7 out of 18 nondepleted patients, but also caused elevations in venous pressure in 9, and resulted in overwhelming acute pulmonary edema in 2 patients. There was an unusual increase in mean weight of patients on either of these regimens.

"Restricting" fluids to an average intake of 0.9 L. *per diem*, resulted in considerable weight loss and thirst, but was effective in preventing hyponatremia in most instances. There was also appreciable urinary loss of potassium. Although none of the patients were embarrassed by pulmonary congestion, two succumbed from serious thromboembolic complications that may have been precipitated by the relative dehydration.

In general these observations were in accord with those of Moore who has described postoperative hyponatremia as due to "sodium paradox," "water intoxication" or excessive loss of sodium from specific lesions[7]. Wilson and associates[8] studied this problem in patients undergoing mitral commissurotomy and found evidence of increased total body sodium and water, and decreased exchangeable potassium preoperatively, as well as hyponatremia in the presence of renal conservation of sodium postoperatively. Goodyer and Glenn[3] attributed much of the hypona-

tremia following mitral valve surgery to the effects of an unusually prolonged antidiuretic stimulus that favored water retention.

Laragh[5] found small amounts of potassium effective in correcting hyponatremia and promoting renal excretion of sodium in nonsurgical patients. Cortisone has been reported to be beneficial in moderating morbidity and mortality to general surgery[4], as well as suppressing the clinical manifestations of rheumatic myocarditis[6]. Accordingly the effects of either potassium or cortisone on morbidity and metabolic responses in subsequent patients form the basis of this report.

**Methods.** Patients were selected for surgery according to the principles previously described[2]. The postoperative fluid management in recent cases has represented a compromise from previous regimens, that is, usually no fluids were administered intravenously after operation, and the oral intake was limited to 1.5 L. *per diem*. Sodium intake was limited to 1 gm. NaCl diet, or a maximum of 17 mEq. *per diem*. Three patients received from 20 to 40 mEq. of potassium as potassium chloride. Nine patients were given cortisone, varying from 25 to 200 mg. *per diem*. One patient, B.J., received only 25 mg. of hydrocortisone injected directly into the pericardial sac just before the operative wound was closed.

External balance* studies were carried out by estimating the oral intake of water, sodium and potassium, as well as collecting 24-hour volumes of pleural drainage and urine for the corresponding outputs. Weights were obtained as early and often as possible under the circumstances. Only 2 patients had appreciable diaphoresis; none had any vomiting or diarrhea.

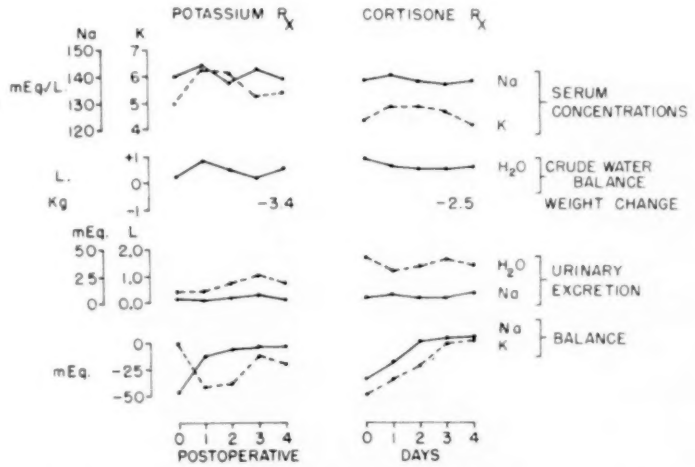


Fig. 1.—Mean daily values for serum sodium and potassium concentrations, crude water balance, change in body weight, 24-hour renal excretion of water and sodium, and sodium and potassium balances of patients treated with either potassium chloride or cortisone. See text for details.

**Results.** 1. EFFECTS OF SUPPLEMENTAL POTASSIUM. Relatively small daily doses of potassium chloride (average 33 mEq.) were accompanied by transient manifestations of mental confusion in 2 out of 3 patients. Serum concentrations of potassium increased to over 6 mEq./L. on the first and second days postoperatively in each patient; none exhibited hyponatremia (Fig. 1). Antidiuresis may have been slightly more marked

*Since both sweat and insensible losses were disregarded, the water balance is designated as "crude water balance," meaning measured intake minus measured output.

than usual, and renal excretion of sodium was not increased. Slightly greater losses of sodium via pleural drainage accounted for a negative sodium balance on the day of operation. Weight loss for the first 4 days averaged 3.4 kg. None of the patients exhibited pericarditis, cardiac or pulmonary complications.

2. EFFECTS OF CORTISONE OR HYDROCORTISONE. Only 1 out of 9 patients exhibited any mental symptoms; this patient developed euphoria, disorientation, confusion and hallucinations on the day after surgery. These symptoms occurred in the individual who received the largest dose of cortisone (200 mg.) and quickly disappeared within hours after discontinuing it.

None of the 9 patients developed either hyponatremia or hyperkalemia (Fig. 1). Renal conservation of sodium was unaffected by cortisone. The average weight loss after 4 days was 2.5 kg. This was comparable to the effects previously observed in patients on a restricted fluid intake.

Hydrocortisone and cortisone appeared to be valuable adjuncts to intensive pressor amine therapy of marked hyperpyrexia, circulatory collapse and heart failure in one patient who developed these complications on the first postoperative day.

**Case Report.** V.P. was a 30-year-old white female with no history of rheumatic fever who was in good health until 29 years of age when she became abruptly ill with chills, fever, and bacteremia due to hemolytic *Staphylococcus aureus*. She was treated vigorously with penicillin for 7 weeks with bacteriologic cure. She never felt well after that, was unable to resume secretarial work and felt chronically fatigued. When first evaluated in March, 1954, she was found to have marked mitral stenosis with slight mitral insufficiency and atrial fibrillation, Class IV-D. She was considered to have carditis and was treated with bed rest, digitoxin, salt restriction, aspirin (4 gm. *per diem*) and phenobarbital. She gradually improved, became ambulatory and was considered ready for surgery when seen again in August.

At operation she was found to have a mitral regurgitant jet. Because of marked valvular calcification, only a modest dilatation of mitral valve orifice was accomplished. She received 2500 cc. of 5% glucose in water during the course of the operation and recovery from anesthesia.

On recovery from anesthesia her condition was satisfactory. The total fluid intake for this day was 2640 cc., and the urinary output was 300 cc. The following morning her condition rapidly became critical with fever rising to 106° F., tachycardia of 170 and blood pressure was unobtainable. There were signs of severe shock and evidence of right heart failure with progressive cardiac dilatation. Her sensorium was depressed, but she could be aroused. Intravenous norepinephrine resulted in profound vasospasm that interrupted venous flow; 10 mg. neosynephrine and 25 mg. hydrocortisone intravenously did not cause this extreme reaction and made it possible to obtain low levels of blood pressure. She was given 0.8 mg. cedilanid intravenously, 200 mg. cortisone and 600 mg. ephedrine sulfate in divided doses over the next several hours with dramatic improvement in her clinical condition.

Following this she improved sufficiently to be ambulated on the seventh day. She was discharged from the hospital on the tenth day, with instructions to take cortisone, 25 mg. twice daily, and to remain on the cardiac regimen of rest, digitoxin and salt restriction. Two weeks after returning home she suddenly developed pulmonary edema, but gradually recovered. Her subsequent course was characterized by chronic illness, fatigue and very poor tolerance for exertion for the next several months.

Five out of 9 patients had conspicuous pericardial friction rubs several days after operation. This persisted for over 2 months in one individual. Another patient required a tracheotomy for the relief of excessive bronchial secretions that impaired pulmonary ventilation; his subsequent course was complicated by atelectasis, pneumonia and pleural effusion with delayed resolution.

**Discussion.** Continued clinical observations of patients recovering from

mitral valve surgery* indicates that the unusual metabolic responses of weight gain (from water retention) and hyponatremia can be prevented by limiting the fluid intake to 1.5 L. *per diem* (Table 1). Supplemental potassium chloride in small amounts did not augment renal excretion of sodium in these patients. Elevation of serum potassium concentration to over 6 mEq./L. during the first 2 postoperative days, when oliguria was normally present, seemed to be hazardous. Consequently, it may be better to provide only very limited amounts of potassium in the form of fruit juices or beef broth as desired and tolerated by the patient (Table 2). Nevertheless, serum sodium and potassium concentrations should be checked on the second postoperative day as a precautionary measure. By the time the patient's hunger is restored, oliguria is replaced by diuresis, and the risk of hyperkalemia appears to be remote.

TABLE 2.—COMPARATIVE VALUES OF COMMON NUTRIENTS[5a]

| | *Na* | *K* | *Calories* |
|---|---|---|---|
| | *(mEq. per 8 ounce serving)* | | |
| Beef broth | 3.6 | 3.5 | 30 |
| Bouillon (canned) | 7.7 | 3.9 | 30 |
| Bouillon (cubes) | 37.6* | 3.6* | 3* |
| Apple juice | 0.4 | 6.2 | 134 |
| Grape juice | 0.1 | 7.4 | 178 |
| Grapefruit juice | 0.07 | 15.4 | 139 |
| Orange juice | 0.3 | 13.5 | 108 |
| Pineapple juice | 0.5 | 8.6 | 130 |
| Prune juice | 0.2 | 16.0 | 190 |
| Tomato juice | 1.9 | 8.0 | 55 |
| Lonalac | 0.4 | 0.4 | 154 |
| Milk | 5.2 | 8.6 | 165 |

*Per cube. Should be used only when there is a specific need for sodium.

TABLE 1.—VARIATIONS IN METABOLIC RESPONSES AFTER MITRAL VALVE SURGERY

| *Postoperative Regimen* | | *Effects Observed Within 5 Days* | | | | |
|---|---|---|---|---|---|---|
| | | | *Sodium* | | *Potassium* | |
| *Mean Fluid Intake L./d.* | *Mean Amount of Supplement Per diem* | *Body Weight* | *Serum Conc.* | *Balance* | *Serum Conc.* | *Balance* |
| 2.5* | — | ↑ | ↓ | — | — | — |
| 2.7* | Sodium, 60 mEq. | ↑ | ↓ | + + | | — |
| 0.9* | — | ↓ ↓ | — | — | — | — |
| 1.5 | Potassium, 33 mEq. | ↓ ↓ | — | — | ↑ ↑ | — |
| 1.5 | Cortisone, 100 mg. | ↓ ↓ | — | — | — | — |

*Previously reported elsewhere[1]. See text for discussion.

Cortisone therapy on a regimen of limited water and sodium intake did not cause venous hypertension or cardiac edema. It may have moderated the hyponatremic response to stress. Actually, it would require administering larger amounts of water to be sure that the lack of hyponatremia was not indeed due to limitation of fluid intake. It may be significant, however, that patient V.P. who received 2.6 L. of water on the day of operation and developed circulatory collapse the following day (with a fluid intake of 1.6 L.) did not develop hyponatremia. Usually hyponatremia was a conspicu-

*An opportunity to evaluate the effects of general anesthesia in these patients was afforded in patient E.W. who developed severe hypotension after induction, and before the operation was started. Operation was cancelled. Although she exhibited many of the clinical manifestations described by Moore[7] for the initial "adrenergic-corticoid" phase, there was no oliguria or hyponatremia.

ous finding in earlier patients under less stressful circumstances.

Since cortisone did not prevent pericarditis, the efficacy of this treatment with respect to anti-inflammatory or antirheumatic effects is questioned. Although these patients appeared to convalesce more rapidly, and exhibited in general less morbidity, it is impossible to differentiate these effects from those related to euphoria. Finally, the beneficial effects of large doses of cortisone and pressor amines in treating hyperpyrexia and circulatory collapse from rapidly developing heart failure were impressive in one patient who became moribund on the first postoperative day. It was all the more remarkable that despite the profound collapse of the circulation, major metabolic disturbances did not ensue.

**Summary.** 1. Clinical observations are reported on the effects of potassium and cortisone supplements on the morbidity and metabolic responses of 12 patients submitted to mitral valve surgery.

2. Administration of limited amounts of potassium was associated with the appearance of mild hyperkalemia in all 3 patients.

3. The administration of cortisone was not accompanied by gain in weight, hyponatremia, or hyperkalemia when fluid and sodium intake were limited in 9 patients. Cortisone appeared to be a useful adjunct to the intensive treatment of profound circulatory collapse with pressor amines in one patient. Cortisone did not prevent postoperative pericarditis.

4. It is concluded that limitations of fluids and sodium are important in the postoperative management of patients submitted to mitral valve surgery. Potassium should be limited to natural sources as tolerated by the patient. Supplementary cortisone may be an adjunct in occasional patients experiencing profound stress.

## REFERENCES

1. **Bruce, R. A., Merendino, K. A., Dunning, M. F., Scribner, B. H., Donohue, D., Carlsen, E. R.,** and **Cummins, J.:** Surg., Gynec. & Obst., **100,** 293, 1955.
2. **Bruce, R. A., Rodgers, D. L., Merendino, K. A., Nielsen, M., Paine, R. M.,** and **Johnson, A. D.:** Northwest Med., **52,** 201, 1953.
3. **Goodyer, A. V. N.,** and **Glenn, W. W. L.:** Circulation, **11,** 584, 1955.
4. **Kinsell, L. W.:** J. Internat. Coll. Surgeons, **21,** 230, 1954.
5. **Laragh, J. H.:** J. Clin. Invest., **33,** 807, 1954.

5a. **MacRae, N.:** Personal communication, 1955.

6. **Massell, B. F.:** New England J. Med., **251,** 183, 221, 263, 1954.
7. **Moore, F. D.:** J. Am. Med. Assn., **154,** 379, 1954.
8. **Wilson, G. M., Edelman, I. S., Brooks, L., Myrden, J. A., Harken, D. E.,** and **Moore, F. D.:** Circulation, **9,** 199, 1954.

*(Interlingua on page 435)*

# THE THYROTOXIC REMNANT

By John H. Nodine, M.D.
ASSISTANT CHIEF, ENDOCRINE CLINICS, PHILADELPHIA GENERAL HOSPITAL

William H. Perloff, M.D.
ASSOCIATE PROFESSOR OF MEDICINE, DIRECTOR, SECTION ON ENDOCRINOLOGY, TEMPLE UNIVERSITY HOSPITAL
CHIEF, ENDOCRINE CLINICS, PHILADELPHIA GENERAL HOSPITAL

Theodore E. Sopp, B.S.
CHIEF PHYSICIST, PHILADELPHIA GENERAL HOSPITAL

Ricardo N. Ferrandis, M.D.
SCHERING FELLOW IN ENDOCRINOLOGY, PHILADELPHIA GENERAL HOSPITAL, 1952–1953

AND

Danilo de Albuquerque, M.D.
ELI LILLY FELLOW IN ENDOCRINOLOGY, TEMPLE UNIVERSITY HOSPITAL, 1953–1954

(From the Endocrine Clinics of the Philadelphia General Hospital and the Section on Endocrinology, Department of Medicine, Temple University School of Medicine, Philadelphia, Pennsylvania)

Radioiodine (I-131) has proved to be an important aid in the evaluation of thyroid gland function. Because the measurements are of such a precise nature, discrepancies between the radioactive tracer tests and the clinical status of the patient may offer a clue to the further understanding of the pathologic physiology of thyroid disease.

Following treatment for thyrotoxicosis with radioiodine or surgical thyroidectomy the 24-hour thyroid uptake of I-131 is usually normal or low. Occasionally, even where the patient is clinically euthyroid or hypothyroid, the radioiodine thyroid uptake has been found to be in the thyrotoxic range. In addition, even when the thyroid uptake is not elevated, the serum hormonal radioiodine level (PBI-131) may be abnormally high. We have studied a number of patients in whom, after treatment for thyrotoxicosis, the clinical status was not consistent with the I-131 thyroid uptake, the circulating PBI-131, or both. Similar instances have been reported in the data of others[2,4-6,11]. We are reporting detailed metabolic studies in 4 such patients as well as partial observations in 2 others.

**Methods.** Patients were given 200 microcuries of I-131 intravenously following which the amount of radioactivity in the thyroid, blood and urine was measured at ½, 1, 2, 3, 6, 12, 24, 48, 72 and 96 hours. Radioactive emanations from the thyroid gland were compared to the original dose. Interval urines were determined by the liquid counting method of Marinelli[8]. Blood radioactivity was measured before and after precipitating the proteins with trichloracetic acid and was compared to standards prepared under identical conditions (to correct for self absorption) from the patient's serum prior to radioactive iodine administration. All blood measurements were done with a gas flow beta-ray counter. These methods will be described in more detail in another publication. Duplicate determinations were performed on all blood specimens and when the combined statistical counting and chemical difference exceeded 5%, they were repeated. Serum protein-bound iodine (PBI) levels were measured by the method of Brown *et al.*[3].

**Case Reports.** CASE 1. W.G., a 39-year-old white male, complained of nervousness, pal-

pitation, weight loss and staring expression since February, 1952. He had been well since a thyroidectomy in 1940 for thyrotoxicosis. The right lobe of the thyroid gland was not palpable; the left lobe consisted of a moderately firm nodule 3 cm. in diameter. Lid retraction was marked and the patient was obviously thyrotoxic. The basal metabolic rate was plus 21% and the 24-hour I-131 thyroid uptake was 48% with an 80% conversion ratio. The thyroid nodule was partially removed in March, 1952, without previous antithyroid or iodine therapy and only a small remnant of thyroid tissue was left in the neck. Histologically, the excised tissue showed such marked hyperplasia that adenocarcinoma could not be ruled out. Subsequent examinations in May and December, 1952, revealed 24-hour I-131 thyroid uptakes of 46 and 54% and serum cholesterols of 270 and 230 mg. per 100 cc. respectively. During this interval of time he was feeling well. In September, 1952, he began to notice increased nervousness and lid retraction, but no weight loss. In December, 1952, a chemical protein-bound iodine was found to be 7.8 mcg. (micrograms) per 100 cc. By February, 1953, his symptoms had become quite pronounced, although he was still thought to be euthyroid by clinical evaluation. The blood pressure was 128/78 and the pulse rate was 84 per minute. His serum protein-bound iodine at that time was 5.3 mcg. per 100 cc. In view of the discrepancy between the 24-hour I-131 thyroid uptake, on the one hand, and the serum PBI and clinical status on the other, the iodine metabolic study described above was undertaken.

Figure 1 shows the fraction of the administered dose of I-131 which was found in the thyroid at any time compared to the range of 15 normal controls. The gland accumulated radioactive iodine more rapidly than normal as can be seen from the increased slope of uptake during the first few hours, resembling in this respect, the thyrotoxic gland. The maximum retention of I-131 in the gland was only slightly above normal but the rate of decline was more rapid than normal. Figure 2 shows the integral urinary radioiodine excretion. The rate of excretion of I-131 during the first hour was normal but rapidly fell below the normal range, so that the total 24-hour excretion was below normal. These findings are consistent with mild thyrotoxicosis. Figure 3 shows the protein-bound I-131 levels of the serum. Significant amounts were found early, and higher than normal values were observed at all times with a maximum level reached by 72 hours. Figure 4 depicts the distribution of the admintered dose of I-131 based upon the assumption that both iodide and protein-bound iodine mix through the estimated extracellular volume[7,10]. The marked increase in the hormonal I-131 fraction of this patient may be compared with that of a normal subject (Fig. 5) and with a patient with thyrotoxicosis (Fig. 6).

The initial dip in the total fraction accounted for is probably due to the dispersal of I-131 into areas which were not measured in this study but from which return to the blood was possible within 12 to 24 hours. Such areas might be stomach, salivary glands and other organs or tissues[7]. The significance of the apparent secondary rise in the free iodide fraction is not certain. It may be due in part to the breakdown of organic to inorganic iodine in the body and in part to loss of PBI during precipitation and washing[9].

CASE 2. M.W., a 21-year-old white male, was seen in August, 1951 with classical Graves' disease. The basal metabolic rate was only plus 12% but the 24-hour I-131 thyroid uptake was 64%, and the serum protein-bound iodine was 10.7 mcg. per 100 cc. Because of marked exophthalmos he was treated with a combination of methylthiouracil, Lugol's solution and desiccated thyroid. By January, 1952 he was clinically euthyroid and his exophthalmos had improved so that he was subjected to a thyroidectomy in February, 1952. At this time approximately 95% of the thyroid gland was removed. In September, 1952 while on no therapy, he was re-evaluated because of "nervousness" and was thought to be clinically myxedematous because of the development of thick dry skin, dry hair

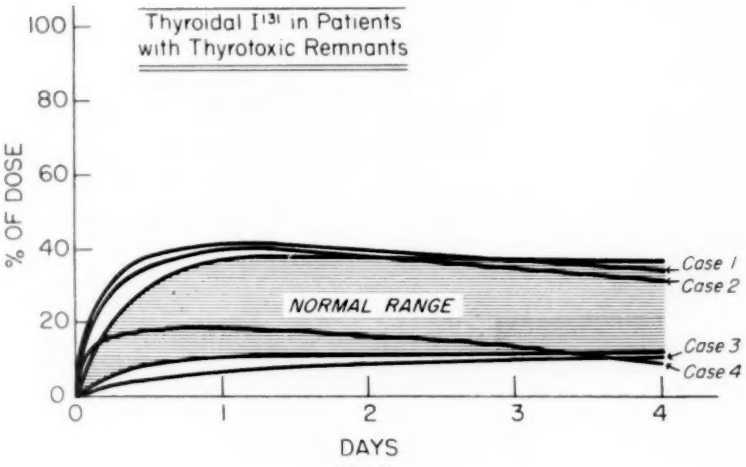


**Fig. 1.**

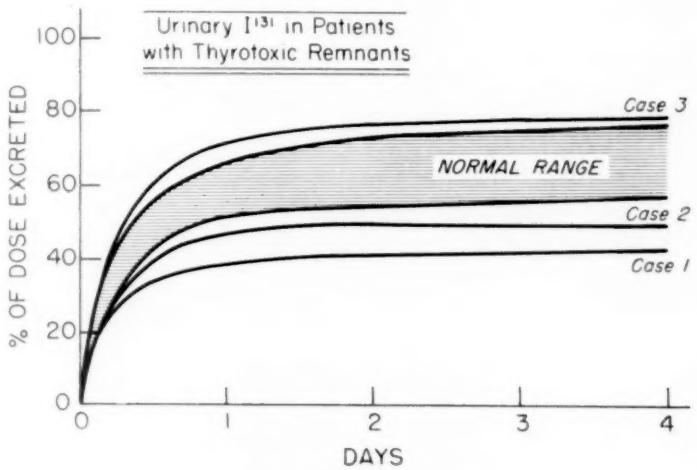


**Fig. 2.**

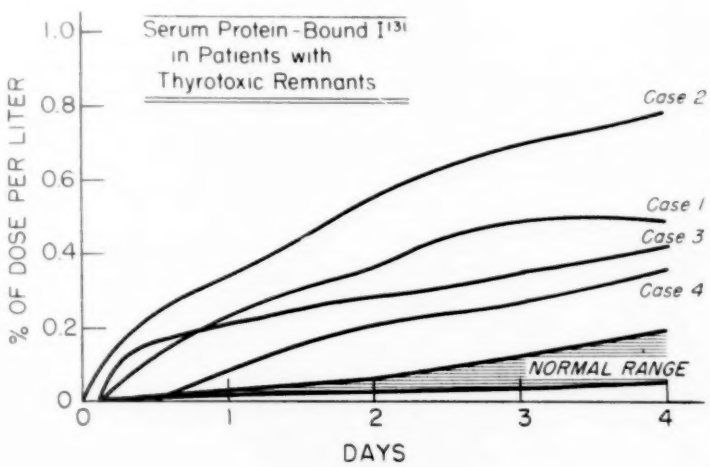


**Fig. 3.**

periorbital edema, and weight gain of 22 pounds. The serum PBI was 3.5 and 4.0 mcg. per 100 cc., but the I-131 thyroid uptake was 37% with a 63% conversion ratio. It was at this time that the I-131 metabolic study was undertaken.

As may be seen in Figs. 1 and 2, the thyroidal and urinary radioiodine fractions are similar to those in Case 1. By the end of ½ hour there was a significant amount of protein-bound I-131 in the blood and the level exceeded that in Case 1 throughout the entire course of the study (Fig. 3). Figure 7 shows the distribution of the administered I-131 to be similar to that in Case 1 (Fig. 4). Again the initial

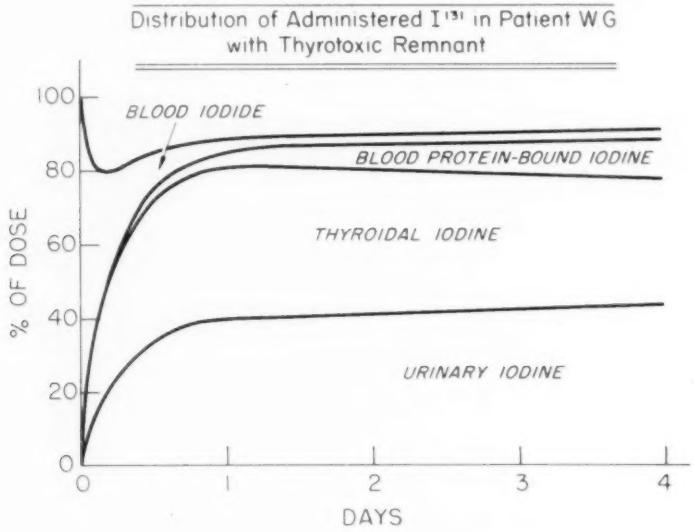


**Fig. 4.**

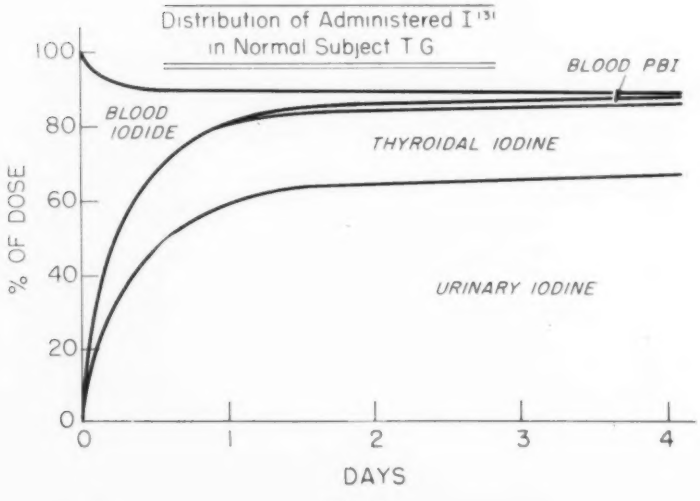


**Fig. 5.**

dip in the total fraction is accounted for and the terminal rise in the extracellular iodide fraction may be seen.

CASE 3. E.A., a 33-year-old colored female, was given 10 millicuries of radioiodine for the treatment of thyrotoxicosis June 8, 1951. Fifteen months later the patient returned to the Endocrine Clinic complaining of fatigue, weight gain and cold intolerance. Her skin and hair were dry and it was felt that mild hypothyroidism had developed. Laboratory studies were as follows: basal metabolic rate, minus 7%; serum cholesterol, 302 mg. per 100 cc.; serum protein-bound iodine, 3.8 mcg. per 100 cc.; and I-131 thyroid uptakes, 5-hour 15%, 24-hour 23%, 48-hour 10%. Three months later the serum cholesterol was 345 mg. per

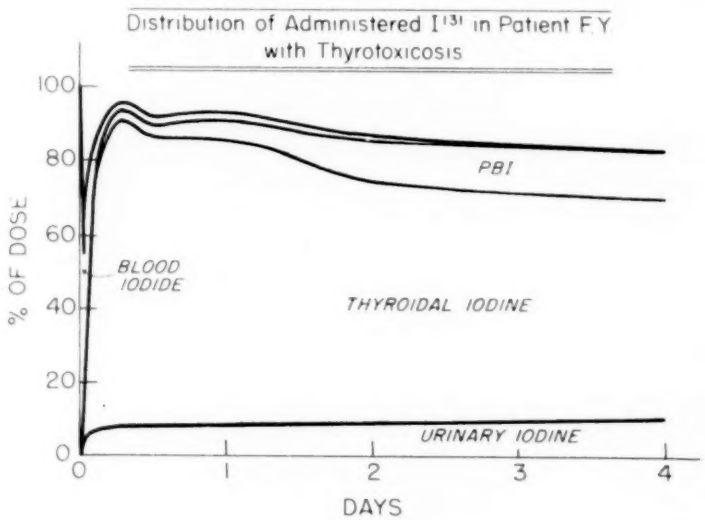


**Fig. 6.**

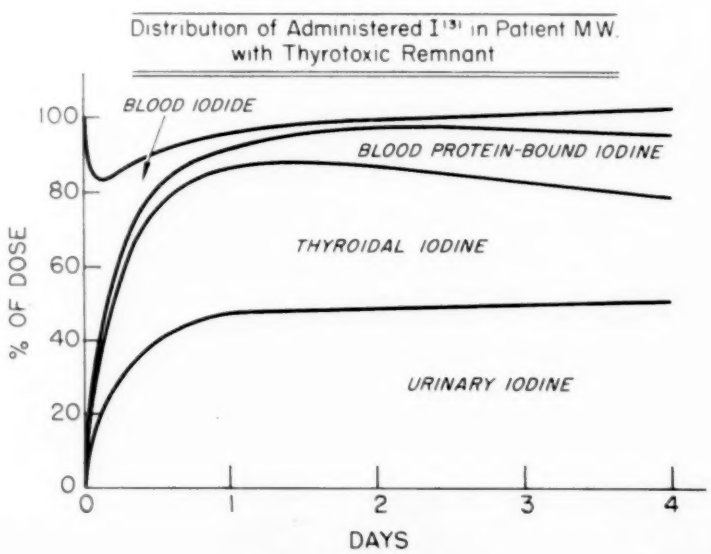


**Fig. 7.**

100 cc. and the thyroid I-131 uptake was 31% at 24 hours. The following month the serum cholesterol was 300 mg. per 100 cc. and the serum PBI was 2.5 mcg. per 100 cc. At this time the I-131 metabolic study was undertaken. Three years after I-131 therapy the 24-hour I-131 thyroid uptake was 29%, the serum cholesterol 300 mg. and the serum protein-bound iodine was 2.5 mcg. per 100 cc. The prompt and dramatic response of symptoms and physical findings to desiccated thyroid therapy at this time confirmed the original clinical impression of hypothyroidism.

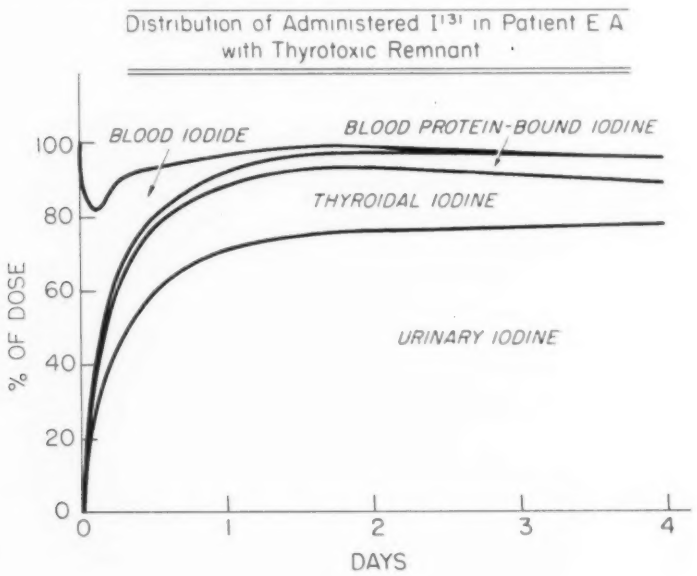


Fig. 8.

The results of the metabolic study are shown in Figs. 1, 2, 3 and 8. The initial I-131 thyroid uptake was rapid, exceeding normal levels during the first few hours (Fig. 1), but the maximum accumulation was within the normal range. The rate of decline was more rapid than normal, so that by 96 hours the thyroid I-131 retention was lower than normal. In this case, the integral urinary excretion of I-131 (Fig. 2) was slightly above the normal range and was consistent with a picture of hypothyroidism. On the other hand, the hormonal radioiodine level (PBI-131) (Fig. 3) was definitely elevated throughout the course of the experiment. In general, the distribution of radioiodine (Fig. 8) resembled that in Cases 1 and 2, especially as regards the increased serum PBI-131 fraction.

CASE 4. E.H., a 69-year-old white female, was referred to the Endocrine Clinic because of weakness, weight loss, dyspnea and myxedema. Her past history was irrelevant except-ing for a thyroidectomy 32 years previously for an undetermined reason. She was thin (weight, 100 pounds; height, 61 in.) and malnourished; her voice was brassy and her mental responses were sluggish. The skin was thick and dry, head hair was coarse and dry, and periorbital edema was prominent. The blood pressure was 95/50 and the pulse rate was 60 per minute. She was obviously a classical case of severe myxedema. The basal metabolic rate was plus 8% and minus 6% on two occasions; the serum cholesterol was 285 mg. per 100 cc.; the 24-hour I-131 thyroid uptake was 7.5% and the serum PBI was 1.5 mcg. per 100 cc.

This patient's inability to cooperate in the proper collection of urines pre-

cluded the accurate determination of the urinary I-131 fraction. Blood and thyroid I-131 measurements were made at the usual time intervals, however (Table 4). Although the thyroid I-131 values were consistently low, as would be anticipated in myxedema (Fig. 1), the serum PBI-131 levels were elevated above normal (Fig. 3). The 24-hour measurement showed 0.14% of the administered I-131 per liter (normal = 0.02 to 0.06) with a 0.44% value at 96 hours (normal = 0.06 to 0.18).

CASE 5. E.R., a 52-year-old white female, was thyroidectomized because of a large nodular goiter which was causing pressure symptoms. One year later she was seen in the Endocrine Clinic with the complaints of fatigue, sluggishness, weight gain and cold intolerance. She was thought to be hypothyroid because of the suggestive history as well as the findings of dry skin and hair.

No basal metabolic rate was performed, but other laboratory studies were as follows: the serum cholesterol was 600 mg. per 100 cc.; the serum PBI was 4 mcg. per 100 cc. and the 24-hour thyroid I-131 uptake was 50%, with elevated PBI-131 levels of 0.3% of the dose per liter at 24 hours and 0.28% at 48 hours (normal = 0.03 to 0.08). Two months after the administration of 60 mg. of U.S.P. thyroid daily, the serum cholesterol fell to 250 mg. per 100 cc. and the presenting symptoms were almost completely relieved.

Despite the clinical hypothyroidism, the low serum protein-bound iodine and the elevated serum cholesterol which fell to a normal level on thyroid therapy, this patient showed an increased 24-hour I-131 thyroid uptake as well as elevated conversion rates at 24 and 48 hours, as manifested by the high PBI-131 values.

CASE 6. A.W., a 47-year-old white female, was thyroidectomized for thyrotoxicosis 15 years previously. She was obviously myxedematous; her skin was thick and dry and head hair was sparse, coarse and dry. She was dull and sluggish and complained of cold intolerance. Moderate exophthalmos was present and lid retraction was marked. This patient was studied at the Temple University Hospital. The basal metabolic rate was minus 34%, the serum cholesterol was 394 mg. per 100 cc. and the serum PBI was 2.7 mcg. per 100 cc. A 24-hour thyroid I-131 uptake study performed by Dr. Robert Robbins was 24% and the conversion ratio at 48 hours was 37%.

Three months after the daily administration of 60 mg. of U.S.P. thyroid, the serum cholesterol was 250 mg. per 100 cc. and the pulse rate had increased from 58 to 88 per minute. The presenting symptoms were completely relieved. This patient was clinically myxedematous and showed a consistently low serum PBI and elevated serum cholesterol levels in the presence of a normal I-131 thyroid uptake and conversion value.

**Discussion.** A review of the data indicates that the radioiodine studies in these patients appear to be inconsistent with either the clinical status or with serum protein-bound iodine levels. The reasons for these discrepancies are not completely clear, but certain possibilities seem likely and others are worth consideration.

An elevated serum PBI-131 level in the face of clinical euthyroidism or even hypothyroidism may be due to low thyroidal iodine stores. This suggestion has been made previously by others[1,6,12]. For example, let us assume that a total daily secretion of 0.2 mg. of hormonal I-127 by the thyroid is required to maintain a patient in the state of euthyroidism. If a gland contained 20 mg. of I-127, this would represent a secretory rate of 1% per day, but if it contained only 2 mg. of I-127 this would represent a secretory rate of 10% per day. If both glands collected I-131 equally, the second gland would be expected to secrete 10 times as much hormonal I-131 as the first and consequently, the serum PBI-131 of one patient would be higher than that of the other, even though the PBI-127 values of both patients were equal and normal. It is apparent that the level of the

thyroidal iodine stores must be taken into consideration in the evaluation of PBI-131 levels, since low thyroidal stores would tend to be associated with high PBI-131 values, and high thyroidal stores with low PBI-131 values even though in each instance the PBI-127 levels were equal.

To test this assumption, the stores of PBI-127 in the thyroid gland of Cases 1 and 2 were estimated as follows:

$$\frac{\text{Thyroid I-127}}{\text{Serum PBI-127}} = \frac{\text{Thyroid I-131}}{\text{Serum PBI-131}}$$

The values for thyroid I-131, serum PBI-127 and serum PBI-131 were measured, and the levels obtained 96 hours after the administration of the radioiodine were used because at that time equilibrium is reached[1]. This calculation assumes that the specific radioactivity of the blood is the same as that of the thyroid gland. By this method of estimation the total hormonal iodine stores of the thyroid in these subjects were 3.2 and 1.5 mg. respectively. If one multiplies the values for these hormonal stores by the fraction of I-131 lost daily by the thyroid gland after the first 48 hours, the actual hormonal secretory rate (hormonal I-127 in micrograms per day per thyroid) is found to be 250 and 130 respectively. Although the absolute significance of these calculations is questionable, the relative values for hormonal secretory rates are consistent with the clinical status of these patients.

The disparity between the thyroidal I-131 fraction and serum PBI-127 is more difficult to understand. The thyroidal fraction of any dose of administered radioiodine consists of the amount present in the thyroid gland at any given time as well as that already secreted by the gland into the blood stream. This happens to be 44% at 96 hours in both Cases 1 and 2, and 53% at 24 hours in Case 5, values which are in excess of our normals (up to 39%). This is independently confirmed by the decreased urinary fractions (Fig. 2). If the same percentage of circulating I-127 were taken up and secreted by the thyroid gland, the serum protein-bound iodine would be expected to be elevated, whereas in these patients it was actually normal or low. A number of possible explanations for this inconsistency may be considered, none of which is completely satisfactory. Blom and Terpstra[2] suggested that the disparity between the elevated thyroid I-131 uptake and the low or normal PBI-127 might be on the basis of a low I-131 clearance. In our patients, however, the reverse was true and the I-131 thyroid clearances were elevated (34 cc./min. between 2 and 6 hours in Patient 1, and 31 cc./min. at the same intervals in Patient 2, in contrast to normal values of 4 to 23 cc./min. with a mean value of 15 cc./min.).

If the amount of I-127 available to the thyroid gland were lower than normal, one might postulate that the gland was trapping and converting a larger than normal percentage of the iodine, as has been postulated in the case of the "iodine-hungry" gland. For example, if a thyroid gland were able to trap and convert 50% of the circulating iodide, it would be able to synthesize twice as much hormone in the patient with a circulating iodide level of 2 mcg. per 100 cc. as in the patient with a level of 1 mcg. per 100 cc. Should this be the correct explanation, the patients described here should have very low concentrations of serum iodide. We have no evidence to bear on this point, but such studies are now in progress. It may be that variations in the uptake of radioiodine by the normal thyroid glands of euthyroid subjects also depend upon the levels of circulating available iodide.

The decreased availability of iodine

to the thyroid gland might occur in several different ways: there might be a deficiency of iodine in the diet. This was ruled out by prescribing small amounts of iodine daily in the form of Lugol's solution to 3 patients prior to the study. Abnormality of gastrointestinal iodine absorption appeared unlikely because in Patients 2 and 5 similar results were obtained after both oral and intravenous administration of I-131. The possibility that the thyroid gland was able to trap iodine and store it temporarily as "loosely-bound" iodine and then to return it to the blood stream was not considered likely since almost all of the radioactivity lost by the thyroid gland was eventually found in the blood as PBI-131. One must also consider the possibility that the thyroid gland may at times be in positive iodine balance and may be accumulating iodine. This would not seem to be the case in our patients, since radioiodine was not being retained by the thyroid gland, and furthermore, Case 2 was followed over the course of 7 months, during which an elevated I-131 fraction was found consistently even though the patient was clinically myxedematous. Finally, it may be that the thyroidal PBI-127 fraction actually is increased but that peripheral utilization has been elevated to an even greater extent, so that the net result is a normal or low serum protein-bound iodine. This interesting but unlikely explanation is being investigated currently.

**Summary.** Radioiodine metabolic studies are reported in 6 patients, 4 of whom had been treated previously by surgical or radioiodine thyroidectomy for thyrotoxicosis. In each instance, the 24-hour I-131 thyroid retention or the hormonal conversion rate, or both, were inconsistent with the clinical status. Of 3 patients with both elevated I-131 thyroid uptakes and hormonal conversion rates, one was clinically euthyroid and 2 were hypothyroid. Two other patients were clinically myxedematous but showed normal thyroid I-131 retentions; one of these also had an elevated conversion rate. The sixth individual was markedly myxedematous and showed a low I-131 thyroid uptake, but the hormonal conversion rate was high.

**Conclusions.** After thyroidectomy for thyrotoxicosis, either surgical or by means of radioiodine, the thyroid retention of a tracer dose of I-131 or the rate of its conversion to radiohormone, or both, may be inconsistent with the clinical status of the patient. An elevated I-131 conversion rate in the patient who is clinically euthyroid or even frankly myxedematous is likely to be related to the low amounts of hormonal iodine stored in the thyroid glands of these individuals. The failure of correlation of the thyroidal fraction of I-131 (that present in the gland as well as the amount already secreted into the blood stream as hormonal radioiodine) and the serum protein-bound iodine level and clinical status is more difficult to understand. Several possible explanations are offered, the most likely of which is a reduced serum iodide level which would tend to decrease the absolute amount of iodine available to the trapping mechanism of the thyroid gland.

APPENDIX. The following 4 tables are presented for the benefit of those readers who are interested in the specific values obtained. The individual figures represent the per cent of the administered dose of radioiodine found in the thyroid gland or body fluids at the recorded time intervals. Figures 4, 7 and 8 in the body of the paper were constructed from Tables 1, 2, and 3 respectively. No figure was constructed from Table 4 because urinary volumes were unreliable; the table refers to patient number 4.

TABLE 1.—CASE 1, W.G.

| *Time in hours* | ½ | *1* | *2* | *3* | *6* | *12* | *24* | *48* | *72* | *96* |
|---|---|---|---|---|---|---|---|---|---|---|
| Thyroid | 8.4 | 13.7 | 17.5 | 23.2 | 31.0 | 38.6 | 41.8 | 39.8 | 36.2 | 34.8 |
| Integral urine | 5.6 | 10.0 | 13.2 | 17.5 | 27.2 | 36.3 | 39.7 | 41.0 | 42.0 | 0.3 |
| Serum Iodide-I-131 | 75.9 | 61.5 | 47.4 | 35.8 | 20.1 | 8.9 | 3.0 | 3.3 | 5.5 | 3.3 |
| Serum PBI-I-131 | 0 | 0 | 0 | 0 | 1.9 | 2.1 | 5.2 | 6.3 | 9.3 | 9.1 |
| Total I-131 accounted for | 89.9 | 85.2 | 78.1 | 76.5 | 80.2 | 85.9 | 89.7 | 90.4 | 93.0 | 90.2 |

Figures refer to the per cent of the administered dose of I-131

TABLE 2.—CASE 2, M.W.

| *Time in hours* | ½ | *1* | *2* | *3* | *6* | *12* | *24* | *48* | *72* | *96* |
|---|---|---|---|---|---|---|---|---|---|---|
| Thyroid | 2.7 | 7.7 | 15.8 | 20.5 | 28.9 | .... | 39.5 | 38.0 | 32.8 | 29.3 |
| Integral urine | 1.8 | 6.3 | 12.9 | 19.5 | 31.4 | 41.9 | 47.6 | 49.0 | 49.6 | 50.4 |
| Serum Iodide-I-131 | 72.5 | 65.8 | 50.0 | 41.8 | 24.6 | 9.1 | 2.0 | 3.9 | 6.3 | 9.0 |
| Serum PBI-I-131 | .7 | 1.1 | 1.5 | 1.5 | 2.5 | 5.3 | 6.7 | 11.1 | 14.1 | 15.7 |
| Total I-131 accounted for | 77.7 | 80.9 | 80.2 | 83.3 | 87.4 | .... | 95.8 | 102.0 | 102.8 | 104.4 |

Figures refer to the per cent of the administered dose of I-131

TABLE 3.—CASE 3, E.A.

| *Time in hours* | ½ | *1* | *2* | *3* | *6* | *12* | *24* | *48* | *72* | *96* |
|---|---|---|---|---|---|---|---|---|---|---|
| Thyroid | 3.5 | 7.5 | 8.7 | 14.5 | 16.0 | 17.9 | 19.5 | 17.7 | 14.7 | 12.6 |
| Integral urine | 8.2 | 13.8 | 22.1 | 28.9 | 44.8 | 59.2 | 71.1 | 76.4 | 78.1 | 78.9 |
| Serum Iodide-I-131 | 82.6 | 64.9 | 50.9 | 38.5 | 28.2 | 13.4 | 3.6 | 0.4 | 0.0 | 0.0 |
| Serum PBI-I-131 | 0 | 0 | 0 | 0 | 2.0 | 2.6 | 3.4 | 4.5 | 5.5 | 6.5 |
| Total I-131 accounted for | 94.3 | 86.2 | 81.7 | 81.9 | 91.0 | 93.1 | 97.6 | 99.0 | 98.3 | 98.0 |

Figures refer to the per cent of the administered dose of I-131

TABLE 4.—CASE 4, E.H.

| *Time in hours* | ½ | *1* | *2* | *3* | *6* | *12* | *24* | *48* | *72* | *96* |
|---|---|---|---|---|---|---|---|---|---|---|
| Thyroid | 0.6 | 0.9 | 1.7 | 1.6 | 2.3 | 3.9 | 6.7 | 9.3 | 10.3 | 10.3 |
| Integral urine | Not available | | | | | | | | | |
| Serum Iodide-I-131 | 59.8 | 48.3 | 43.3 | 41.6 | 35.3 | 29.6 | 17.6 | 7.0 | 2.9 | 0.9 |
| Serum PBI-I-131 | 0 | 0 | 0 | 0 | 0 | 0 | 0.9 | 2.4 | 3.0 | 4.3 |
| Total I-131 accounted for | Not available | | | | | | | | | |

Figures refer to the per cent of the administered dose of I-131

ACKNOWLEDGMENT: We are grateful to Margaret Rappoport, R.N., and Edith Robinson, R.N., for their untiring efforts and valuable assistance in the management of patients and the collection of specimens and to the Ciba Pharmaceutical Products, Inc. and the Schering Corporation for their generous financial aid.

## REFERENCES

1. **Berson, S. A.,** and **Yalow, R. S.:** J. Clin. Invest., **33,** 1533, 1954.
2. **Blom, P. S.,** and **Terpstra, J.:** J. Clin. Endocrinol. & Metab., **13,** 989, 1953.
3. **Brown, H., Reingold, A. M.,** and **Samson, M.:** Ibid., **13,** 444, 1953.
4. **Chapman, E. M., Maloof, F., Maisterrena, J.,** and **Martin, J.:** Ibid., **14,** 45, 1954.
5. **Goodwin, J. F., Macgregor, A. G., Miller, H.,** and **Wayne, E. J.:** Quart. J. Med., N.S. **20,** 353, 1951.
6. **Ingbar, S. H., Freinkel, N., Hoeprich, P. D.,** and **Athens, J. W.:** J. Clin. Invest., **33,** 388, 1954.
7. **Leblond, C. P.:** J. Am. Pharmaceutical Assn. (Sci. ed.), **40,** 595, 1951.
8. **Marinelli, L. D.,** and **Hill, R.:** Studies on Dosage in Cancer Therapy. Brookhaven National Laboratory Symposium on Radioiodine. Upton, N. Y.: Associated Universities, Inc., 1948.
9. **Morton, M. E., Chaikoff, I. L., Reinhardt, W. O.,** and **Anderson, E.:** J. Biol. Chem., **147,** 757, 1943.
10. **Myant, N. B.,** and **Pochin, E. E.:** Clin. Sci., **9,** 421, 1950.
11. **Oddie, T. H.,** and **Scott, R. K.:** Brit. J. Radiol., **22,** 348, 1950.
12. **Stanberry, J. B., Brownell, G. L., Riggs, D., Perinetti, H., Delcastillo, E.,** and **Stoiz, J.:** J. Clin. Endocrinol., **12,** 191, 1952.

## SUMMARIO E CONCLUSIONES IN INTERLINGUA

### Le Risiduo Thyrotoxic

Es reportate studios del metabolismo de iodo radioactive in un gruppo de 6 patientes. Le gruppo includeva 4 patientes qui previemente habeva essite tractate pro thyrotoxicosis per medio de thyroidectomia chirurgic o a iodo radioactive. In omne casos del serie integre le retention thyroidic de I-131 post 24 horas o le rapiditate del conversion hormonal o ambes se trovava non de accordo con le stato clinic. Inter le 3 patientes con augmentate retention thyroidic de I-131 e plus accelerate conversion hormonal, 1 esseva clinicamente euthyroide e 2 hypothyroide. Le gruppo etiam includeva 2 patientes qui esseva clinicamente myxedematose sed monstrava normal retention thyroidic de I-131. Un de istes habeva etiam un accelerate conversion hormonal. Le sexte individuo del gruppo esseva marcatemente myxedematose. Ille monstrava un basse retention thyroidic de I-131 sed su conversion hormonal esseva accelerate.

Post thyroidectomia effectuate chirurgicamente o per medio de iodo radioactive, le retention de un dose traciatori de I-131 o le rapiditate de su conversion in radiohormon o ambes pote esser in disaccordo con le stato clinic del patiente. Un accelerate conversion de I-131 in un patiente qui es clinicamente euthyroide o mesmo francamente myxedematose es multo probabilemente un consequentia del basse quantitate de iodo hormonal immagazinate in le glandulas thyroide. Il es plus difficile comprender le absentia de correlation del fraction thyroidic de I-131 (le I-131 presente in le glandula e etiam le quantitate de I-131 jam secernite a in le circulation sanguinee in le forma de radio-iodo hormonal) e del nivello de iodo ligate a proteina seral con le stato clinic del patiente. Plure possibile explicationes es presentate. Le plus plausibile inter illos postula que un reducite nivello de iodido seral tende a reducer le quantitate absolute de iodo disponibile al mechanismo attrappatori del glandula thyroide.

# EFFECTS OF RAUWOLFIA SERPENTINA IN PATIENTS WITH HYPERTENSION*

By H. Brooks Cotten, M.D.

Wood S. Herren, M.D.

Wallace C. McAdory, B.S.

AND

Margaret S. Klapper, M.D.

(From The Department of Medicine and Outpatient Clinic, Medical College of Alabama, Birmingham, Alabama)

Wilkins first introduced the use of *Rauwolfia serpentina* in the United States for the treatment of hypertension in 1952[13]. Many studies confirming the efficacy of this drug and its derivatives in lowering the blood pressure in certain hypertensive patients have since been reported. Because of the effectiveness of this agent, and the paucity and mildness of side effects, Livesay *et al.*, and Finnerty have advocated the use of *Rauwolfia serpentina* in preference to barbiturate sedation in patients with mild hypertension[1,5]. Others have demonstrated its value in increasing the effectiveness and decreasing the undesirable side effects of more powerful antihypertensive agents[1,14,15].

Reduction of blood pressure by these drugs is the result of decrease in the peripheral vascular resistance to blood flow[12]. However, cardiac work is dependent upon the cardiac output as well as the peripheral resistance. We therefore felt it would be of interest to determine the effect of Rauwolfia on cardiac output by applying the formula recently devised by Starr[10,11] to our data.

It is the purpose of this report to summarize our experience with this agent, emphasizing not only the hypotensive response to therapy, but also the slowing of the heart rate. This drug-induced bradycardia may prove to be an indication for the use of *Rauwolfia serpentina* in many patients with cardiac hypertrophy or dilatation due to causes other than hypertension.

**Materials and Methods.** Ninety-eight patients were treated on an outpatient basis at the Hypertensive Clinic of the Medical College of Alabama. See Table 1 for their distribution according to sex and race. Their ages ranged from 21 to 85 years with an average of 53.8 years.

After a complete history and physical examination, initial studies included a blood count, urinalysis, blood urea nitrogen determination, urinary concentration and 15-minute phenolsulfonphthalein tests, electrocardiogram, chest roentgenogram and intravenous

*This work was made possible by grants from the Irwin Neisler Company, Decatur, Illinois, Ciba Pharmaceutical Products, Inc., Summit, New Jersey, and Burroughs, Wellcome & Company, Inc., Tuckahoe, New York.

The Rauwolfia preparations in this report were supplied as Serpasil by Ciba Pharmaceutical Products, Inc., Summit, New Jersey, and Raudixin by E. R. Squibb & Sons, New York, New York.

We wish to express our appreciation to the following medical students for their invaluable help in the Hypertensive Clinic: James Russell, George Irons, Martin Litwin, James McElroy, and Hollis Keel.

TABLE 1.—CLINICAL DATA, HYPOTENSIVE EFFECT, AND HEART SLOWING ACTION OF RAUWOLFIA

| *Degree of Hypertension* | *Number of Patients* | *Sex* | | *Race* | | *Renal Disease* | *Cardiac Disease* | *Cerebral Complications* | *Decreased Pulse 10 beats* |
|---|---|---|---|---|---|---|---|---|---|
| | | *Male* | *Female* | *Colored* | *White* | | | | |
| **Mild** (Diastolic pressure of 90 to 110) | 25 | | | | | | | | |
| Responsive | 12 | 5 | 7 | 6 | 6 | 1 | 8 | 0 | 8 |
| Unresponsive | 13 | 7 | 6 | 8 | 5 | 1 | 9 | 4 | 7 |
| **Moderate** (Diastolic pressure of 111 to 125) | 37 | | | | | | | | |
| Responsive | 15 | 6 | 9 | 15 | | 10 | 10 | 1 | 8 |
| Unresponsive | 22 | 4 | 18 | 14 | 8 | 9 | 18 | 4 | 10 |
| **Marked** (Diastolic pressure higher than 125) | 36 | | | | | | | | |
| Responsive | 24 | 5 | 19 | 20 | 4 | 13 | 22 | 4 | 12 |
| Unresponsive | 12 | 4 | 8 | 11 | 1 | 4 | 11 | 3 | 5 |
| **Total** | 98 | 31 | 67 | 74 | 24 | 38 (38.8%) | 78 (79.6%) | 16 (16.3%) | 50 |
| Responsive | 51 | 16 | 35 | 41 | 10 | 24 | 40 | 5 | 28 |
| Unresponsive | 47 | 15 | 32 | 33 | 14 | 14 | 38 | 11 | 22 |

pyelogram, and in a majority of the patients, a Regitine° test. Re-evaluation studies were obtained at 6-month intervals, or sooner if indicated.

Before institution of therapy with derivatives of *Rauwolfia serpentina*, the average control blood pressure and pulse rate were determined over a period of weeks under mild barbiturate sedation. The pressures and pulse rates were obtained with the patient in a sitting position after resting quietly for a few minutes. The disappearance of sounds was recorded as the diastolic pressure. The degree of severity of hypertension was classified according to the diastolic pressure alone. An average diastolic pressure of 90 to 110 mm. Hg was considered as indicative of a mild degree of hypertension. A diastolic pressure of 111 to 125 mm. Hg was classified as moderate hypertension. Average diastolic values above 125 mm. Hg were designated as severe hypertension. Patients with average diastolic pressures less than 100 mm. were not included in this series. No patients with malignant hypertension were treated with Rauwolfia alone. Patients with auricular fibrillation were not included because of difficulty in determining the blood pressure with accuracy.

Fifty-four patients were treated with reserpine (Serpasil) and 44 patients received the whole root preparation (Raudixin). Therapy was initiated with low dosage and increments in dosage were made at intervals of two or more weeks, depending upon the hypotensive effect obtained or the development of pronounced side effects. For this study, maximum daily dosage levels were arbitrarily limited to 1 mg. of Serpasil or 1 gm. of Raudixin. Larger doses rarely prove to be more effective, but are generally associated with intolerable side effects[6,16]. All patients receiving the effective, the maximal, or the maximal tolerated dosage of these derivatives of Rauwolfia for a minimum of 6 weeks were included. The duration of therapy on the optimal dosage varied from 6 to 35 weeks with an average of 14.5 weeks. If the average blood pressure after attaining the maximum dosage, or the maximal tolerated dosage, still exceeded the normotensive level of 150/90 mm. Hg (mean pressure of 110), a combination of Rauwolfia with other antihypertensive therapy was usually instituted. Some patients with severe symptomatic or progressive hypertension were started on combined therapy before 6 weeks had elapsed, and will be included in a later report evaluating combination therapy.

Results of therapy were evaluated by means of alteration in the mean blood pressure. The mean pressure was calculated as the average diastolic pressure plus 1/3 of the average pulse pressure. The hypotensive effect was classified as responsive if there was a decrease of 20 mm. Hg in the mean blood pressure, or if the normotensive level of 150/90 (mean pressure of 110) was achieved.

The stroke volume was calculated on each patient from the average values for blood pressure before and after therapy according to the formula recently devised by Starr[10,11]: Stroke volume (cc.) = 100 + 0.5 pulse pressure (mm. Hg) — 0.6 diastolic pressure (mm. Hg) — 0.6 age (years).

The cardiac output per minute was obtained by multiplying the stroke volume by the average pulse rate before and after therapy.

**Results.** No significant difference between the effects of Raudixin and Serpasil was noted.

HYPOTENSIVE EFFECT. Of the 98 patients in this study, 25 were classified as having mild hypertension, 37 had moderate and 36 had marked elevation of the diastolic pressure. Of the entire group, 38.8% showed laboratory evidence of significant renal disease, as evidenced by hyposthenuria, azotemia, abnormal PSP tests or intravenous pyelograms. Clinical, electrocardiographic or roentgenographic findings of cardiac disease were found in 79.6%. Cerebral vascular accidents had occurred in 16.3%. The clinical data, and the hypotensive response and bradycardic effects of Rauwolfia are summarized in Table 1.

A significant lowering of blood pressure occurred in approximately half of the patients treated. Of the 12 responsive patients classified before treatment as mildly hypertensive, 8 became normotensive. The remaining 4 patients continued to show blood pressures slightly above the normal level. Fifteen patients having moderate hypertension showed a significant decrease in mean pressure and were classified as

°The Regitine was supplied through the courtesy of Ciba Pharmaceutical Products, Inc.

mildly hypertensive after therapy. Of 25 patients with severe hypertension who showed a significant hypotensive response, 7 became only moderately hypertensive, 15 were mildly hypertensive, and 2 were normotensive after treatment. Review of the clinical data revealed no valid criteria upon which to base a prediction of a satisfactory hypotensive response to therapy.

HEART SLOWING EFFECT. A decrease in pulse rate greater than ten beats per minute occurred in 50 of the 98 subjects treated with Rauwolfia. This effect appears to be unrelated to the hypotensive response. It was present in 22 of the 47 patients who showed no significant decrease in blood pressure, and was present in only 28 of the 51 patients who showed a satisfactory hypotensive response to therapy.

TABLE 2.—CARDIAC OUTPUT OF PATIENTS TREATED WITH RAUWOLFIA, AS CALCULATED FROM STARR'S FORMULA

| | | *Hypotensive Effect* | | *Bradycardic Effect* | |
|---|---|---|---|---|---|
| *Stroke Volume* | *Number of Patients* | *Responsive* | *Unresponsive* | *Present* | *Absent* |
| Unchanged* | 23 | 12 | 11 | 17 | 6 |
| Increased | 54 | 30 | 24 | 28 | 26 |
| Decreased | 21 | 9 | 12 | 5 | 16 |
| *Minute Cardiac Output* | | | | | |
| Unchanged* | 22 | 11 | 11 | 12 | 10 |
| Increased | 25 | 14 | 12 | 7 | 19 |
| Decreased | 51 | 26 | 24 | 29 | 19 |

*The stroke volume and minute outputs were designated as unchanged if the posttreatment values did not differ from the control values by more than 10%.

EFFECT ON CARDIAC OUTPUT AS CALCULATED FROM STARR'S FORMULA. Figure 1 demonstrates that 68 patients showed an increase in stroke volume after treatment. However, as shown in Table 2, the increase was greater than 10% of the pretreatment value in only 54. In 58 patients there was a decrease in cardiac output per minute. The decrease exceeded 10% of the control value in 51. Changes in stroke volume and cardiac output per minute as determined by this method showed no correlation with the effects of therapy on blood pressure or pulse rate.

SIDE EFFECTS. The majority of patients experienced mild nasal congestion on initiation of Rauwolfia therapy which gradually subsided over a period of several weeks. Most patients noted a mild sedative effect, but this was rarely considered objectionable. In the dosages used we did not encounter mood depression of such severity that therapy had to be discontinued. A few patients complained of unusual dreaming but this rarely necessitated reduction in dosage. In one patient afflicted with severe arteriosclerotic paralysis agitans, there was marked improvement in the tremor as the result of Rauwolfia therapy. Our results confirmed Winsor's experience wherein side effects were minimized by increasing the dosage level by small increments[16].

**Comment.** Pharmacologic studies[7,16] indicate that Rauwolfia produces its effects through action on the central rather than the peripheral portion of the autonomic nervous system. It is not an efferent autonomic blocking agent, and does not interfere with postural vascular reflexes. It will not lower the blood pressure below normal levels. The sinus bradycardia produced

by Rauwolfia is not the result of direct action on the heart, and does not appear to be of vagal origin[5].

Though bradycardia is always mentioned as a side effect of *Rauwolfia serpentina* therapy, the desirability of this feature of its action has received little emphasis except with reference to the prevention of tachycardia resulting from more powerful antihypertensive drugs. Experimental studies[9] have shown that cardiac work is greater at rapid than at slow rates, if the minute cardiac output and peripheral resistance remain constant. This is corroborated clinically when young normal individuals develop heart failure in association with prolonged attacks of paroxysmal auricular tachycardia. The deleterious effects of tachycardia are a) increased oxygen utilization resulting from the increased rate, b) reduction in coronary blood flow because of shortened diastole, and c) reduced time for myocardial recovery because of shortened diastole. Conversely, bradycardia is beneficial because cardiac efficiency is increased, coronary blood flow is enhanced, and lengthened diastole favors myocardial recovery. So far as ejection is concerned, the heart wastes energy with each beat during isometric systole when intraventricular pressure must be raised from the zero diastolic level to the level at which the semilunar valves open. Therefore, at constant cardiac output per minute, the heart wastes less energy when the rate is slow.

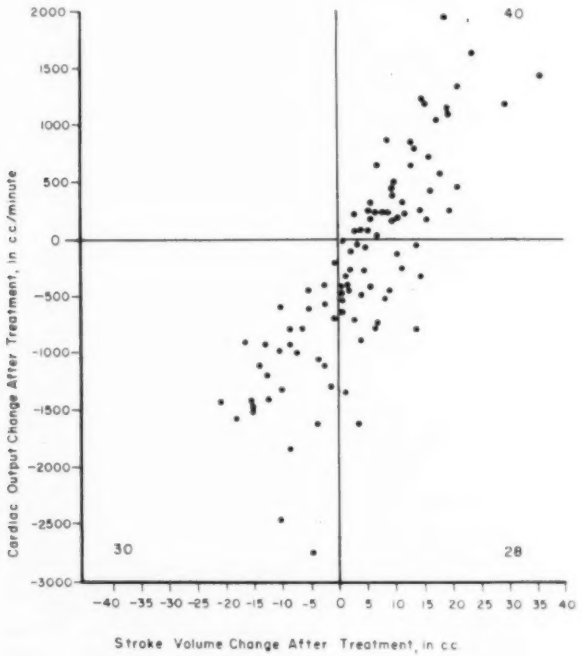


Fig. 1

In the heart characterized by hypertrophy of the myocardial fibers, there is an actual decrease in the concentration of capillaries[8]. It has been suggested on good evidence that brady-

cardia allows better diffusion of oxygen through interstitial fluids and hypertrophied myocardial fibers[1]. Harrison[3] concluded that the optimum cardiac rate for most patients with enlarged hearts is considerably less than that for normal hearts. He suggested that use of drugs producing slowing of the heart rate might be very beneficial in the treatment of the failing heart. Since approximately half of patients receiving Rauwolfia show bradycardia, and since it has been shown that this agent will not lower blood pressure below normotensive levels, it would appear rational to use the drug as an adjunct in the treatment of cardiac hypertrophy and dilatation resulting from many causes other than hypertension. It would seem unwise to attempt to produce bradycardia in association with aortic insufficiency where an increased heart rate may be beneficial[3].

The validity of the formula devised by Starr for determination of the cardiac output from blood pressure and age remains to be proven. His studies suggest that this method is reliable in elderly subjects when the blood pressures are determined with the patient in a supine position. However, use of the formula in younger persons whose blood pressures are obtained in a sitting position, and in those with such complications as chronic congestive heart failure and diabetes, may be unreliable. Our purpose in using this method was to detect any possible broad relationships between gross changes in stroke volume and minute output and unquestioned hypotensive and bradycardic responses to Rauwolfia. We do not feel that the method has been sufficiently tested to allow drawing more exact conclusions.

Gruber[2] long ago demonstrated that sedatives are effective in lowering blood pressure. However, continuous therapy results in loss of this hypotensive effect. Since Wilkins has shown that tolerance to the hypotensive action of derivatives of *Rauwolfia serpentina* does not develop[14,15], prolonged treatment with these agents is more rational than the time-honored use of barbiturates. It is hoped that future widespread prescription of the Rauwolfia derivatives will decrease markedly the cost of their prolonged administration, at present the only deterrent to their use in many patients.

**Summary and Conclusions.** 1) Approximately half of a series of 98 ambulatory patients with hypertension showed a significant lowering of blood pressure as the result of Rauwolfia therapy.

2) Almost an equal number of patients showed a definite slowing of the heart rate which was apparently unrelated to the hypotensive effect. Bradycardia is desirable in most patients with cardiac hypertrophy, whether due to hypertension or other causes, and may serve as an indication for Rauwolfia therapy distinct from its hypotensive or sedative actions.

3) The stroke volume and cardiac output were determined by Starr's formula from the patient's age, average blood pressure, and heart rate. After therapy a majority of patients showed an increase in stroke volume and a decrease in output per minute. There was no apparent correlation between changes in stroke volume and cardiac output per minute and the hypotensive or bradycardic effects of Rauwolfia therapy.

4) Where effective, Rauwolfia derivatives are the treatment of choice in mild hypertension and have definite advantages over time-honored barbiturate therapy.

REFERENCES

1. **Finnerty, F. A., Jr.:** Am. J. Med., **17**, 629, 1954.
2. **Gruber, C. M., Shackelford, H. H.,** and **Ecklund, A. M.:** A.M.A. Arch. Int. Med., **36**, 366, 1925.
3. **Harrison, T. R.:** Failure of the Circulation. 2nd ed. Baltimore: Williams & Wilkins Co., 1939.
4. **Hill, A. V.:** Proc. Roy. Soc. London, Series B, **104**, 41, 1929.
5. **Livesay, W. R., Moyer, J. H.,** and **Miller, S. I.:** J. Am. Med. Assn., **155**, 1027, 1954.
6. **Moyer, J. H.:** Ann. New York Acad. Sci., **59**, 82, 1954.
7. **Plummer, A. J., Earl, A., Schneider, J. A., Trapold, J.,** and **Barret, W.:** Ann. New York Acad. Sci., **59**, 8, 1954.
8. **Roberts, J. T.,** and **Wearn, J. T.:** Am. Heart J., **21**, 617, 1941.
9. **Starling, E. H.,** and **Visscher, M. D.:** J. Physiol., **62**, 243, 1926.
10. **Starr, I.:** Circulation, **9**, 664, 1954.
11. **Starr, I., Schnabel, T. G., Jr., Askovitz, S. I.,** and **Schild, A.:** Ibid., **9**, 648, 1954.
12. **Trapold, J. H., Plummer, A. H.,** and **Yonkman, F. F.:** J. Pharmacol. & Exper. Therap., **110**, 205, 1954.
13. **Wilkins, R. W.:** Ann. Int. Med., **37**, 1144, 1952.
14. Idem: Am. J. Med., **17**, 703, 1954.
15. **Wilkins, R. W.,** and **Judson, W. E.:** New England J. Med., **248**, 48, 1953.
16. **Winsor, T.:** Ann. New York Acad. Sci., **59**, 61, 1954.

## SUMMARIO E CONCLUSIONES IN INTERLINGUA

### Effectos de Rauwolfia Serpentina in Patientes con Hypertension

1. Circa 50 pro cento de un serie de 98 patientes ambulatori con hypertension monstrava un significative reduction del pression sanguinee in consequentia de therapia a *Rauwolfia*.

2. Quasi le mesme procentage de patientes monstrava un definite deceleration del corde, lo que esseva apparentemente non-relationate con le effecto hypotensive. Proque bradycardia es desirabile in le majoritate del patientes con hypertrophia cardiac, tanto quando iste hypertrophia resulta de hypertension como etiam quando illo ha altere causas, nos ha hic un area de possibile usos del therapia a *Rauwolfia* ultra le casos in que iste therapia es indicate a causa de su effectos hypotensive o sedative.

3. Le volumines cardiac per pulso e per minuta esseva calculate secundo le formula de Starr super le base del etate del patiente, del pression median de su sanguine, e de su rapiditate cardiac. Post le therapia le majoritate del patientes monstrava un augmento del volumine per pulso e un diminution del volumine per minuta. Il existeva nulle patente correlation inter le combiamentos del volumines per pulso e per minuta e le effectos hypotensive o bradycardial del therapia a *Rauwolfia*.

4. In casos de leve hypertension, in que derivatos de *Rauwolfia* es efficace, illos es le tractamento a seliger. In tal casos illos ha clar avantages super le therapia traditional a barbiturato.

# CLINICAL EXPERIENCE WITH A NEW COMBINATION OF HYPOTENSIVE AGENTS

By Charles William Smith, M.D.

Kenneth E. Quickel, M.D.

Arthur E. Brown, M.D.

and

Chester G. Thomas, M.D.

(From the Harrisburg Clinic, Harrisburg, Pennsylvania)

Although many drugs are known to possess hypotensive properties, there is yet no single satisfactory specific remedy for hypertension[5]. A prominent reason for this is that hypertension itself is not a specific disease. The term connotes more than the mere presence of elevated blood pressure. It indicates a complex series of etiological factors.

We feel that, although a humoral element is undoubtedly present, hypertension is primarily evoked and reinforced by stimuli traveling numerous pathways in the nervous system. From a pharmacological viewpoint, the hypotensive efficacy of a drug depends merely on its ability to block these pathways. Clinically, however, the demands are more stringent. The blockade produced must strike a delicate balance; neither too weak nor too strong, too limited nor too extensive. To date, no single agent is known which satisfies these criteria.

In recognition of this, much current investigation has centered on combining known hypotensive drugs in an effort to enhance their therapeutic effect without correspondingly increasing their side effects. Wilkins[15] and Fries[7] have reported strikingly better results with combinations of drugs, and their findings have encouraged further efforts at refining the technique of polytherapy.

Recently we have had the opportunity of studying a new preparation incorporating fixed ratios of three hypotensive agents in a single capsule. Because the ratio of drugs is fixed, this comprises a variation from the original concept of combined therapy. In the latter, the usual procedure has consisted of starting each patient on the mildest of the hypotensive agents, usually Rauwolfia, and then gradually adding small increments of more potent drugs until the desired response was attained; in effect, titrating each drug in each patient. The potential advantages of a prearranged ratio are obvious. However, investigation was necessary to determine whether these drugs in these proportions actually constituted a usable, effective hypotensive preparation.

The preparation* consists of the following:

*Formula A*

| | |
|---|---|
| *Rauwolfia serpentina* (crude root) | 25.0 mg. |
| Protoveratrine | 0.2 mg. |
| Phenoxybenzamine (Dibenzyline) | 5.0 mg. |

An alternate dosage strength (Formula B) containing half quantities of each component was also used.

*Mio Pressin (formerly "DRP") supplied by Smith, Kline & French Laboratories, Philadelphia, Pennsylvania.

Figure 1 summarizes the theoretical action of the three components. As shown, the combination should provide a multiple attack on the mechanisms maintaining hypertension by acting simultaneously through the hypothalamic sympathetic centers and the vagal reflexes, and by producing peripheral adrenergic blockade.

The specific virtues and shortcomings of each component are as follows: RAUWOLFIA SERPENTINA. The actions

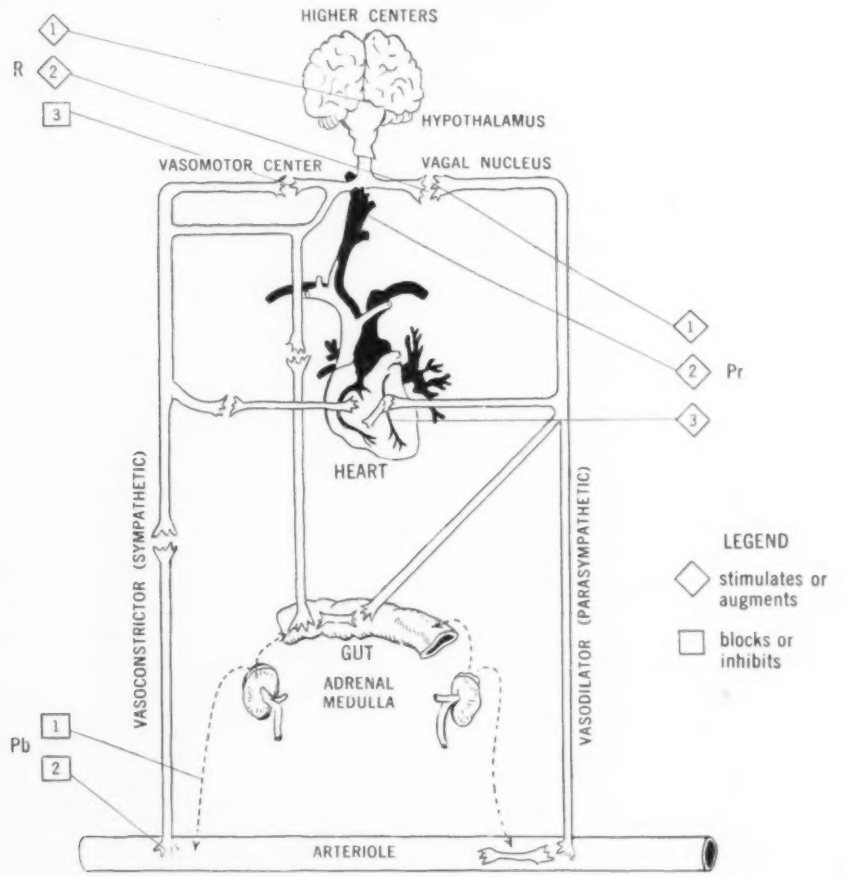


Fig. 1.—Pharmacological action.

R. (Rauwolfia)
1. Augments central control of vasopressor centers.
2. Stimulates receptors in vagal nucleus, producing reflex bradycardia and vasodilation.
3. Inhibits effect of excitatory afferent impulses.

Pr. (Protoveratrine)
1. Stimulates receptors in vagal nucleus, producing reflex bradycardia.
2. Stimulates receptors in carotid sinus reinforcing Pr 1.
3. Stimulates receptors in heart and large vessels, further augmenting Pr 1 and Pr 2.

Pb. (Phenoxybenzamine)
1. Blocks pressor effect of circulating epinephrine.
2. Blocks sympathetic excitatory effector cells.

of this drug are best explained as a partial suppression of the activity of the sympathetic centers in the hypothalamus. This site of action would account for the occasionally observed damping of emotional response and the lowering of body temperature, as well as the cardiovascular and ocular signs of sympathetic blockade.

Chronic oral administration of Rauwolfia results in a gradual fall in blood pressure, slowing of heart rate, mild sedation and usually nasal stuffiness. Side effects of mild diarrhea and increased appetite occasionally occur. Rauwolfia is most effective in mild hypertension, or as an adjunct to more potent drugs[16,17]. Clinical studies have revealed no significant difference between the hypotensive activity of the whole root and purified extracts[18].

PROTOVERATRINE. This veratrum alkaloid produces hypotension, cardiac slowing and respiratory depression in animals by reflex mechanisms[1,12] often referred to loosely as the "Bezold-Jarisch effect." The reflexes involve receptors in the heart, carotid body and sinus, and pulmonary vascular bed, and are mediated principally through the vagus nerve[1].

Protoveratrine has no direct vasodilating action of blood vessels when given intra-arterially. It does not block the peripheral effects of epinephrine nor is it a ganglionic blocker. Certain reflexes, such as the pressor response to carotid sinus occlusion, are blocked. The most important side effect of the veratrum alkaloids is nausea and vomiting. This is apparently a central rather than a local gastrointestinal effect, since it follows parenteral as well as oral administration.

In hypertensive patients, intravenous doses of 0.1 to 0.2 mg. of protoveratrine produce a marked drop in blood pressure, slowing of cardiac rate, and relief of symptoms of encephalopathy[10,11]. Orally, it has been found effective in many patients[3,9], but doses must be carefully adjusted for each patient to prevent nausea and vomiting. Almost all patients experience these side effects at some time during therapy. However, postural hypotension, a relatively frequent occurrence with ganglionic or adrenergic blockers, is not a problem, since protoveratrine leaves intact the reflexes maintaining blood pressure in the upright position.

PHENOXYBENZAMINE (DIBENZYLINE). This drug is an orally-effective long-acting adrenergic blocking agent. In cats, oral doses of 10 mg./kg. block the pressor effect of high doses of epinephrine; the blockade is complete within 3 hours and lasts for 24 to 48 hours[6]. The inotropic and chronotropic effects of epinephrine on the heart are not blocked, nor are its inhibitory effects on gastrointestinal or other smooth muscle. "Excitatory" effects of epinephrine or sympathetic stimulation, such as contraction of the nictitating membrane and pupillary dilation, are blocked. Peripheral blood flow is increased by release of normal sympathetic tone. Phenoxybenzamine acts peripherally, rather than centrally on the ganglia, blocking the smooth muscle receptors for endogenous or exogenous epinephrine. It does not affect the parasympathetic nervous system.

Phenoxybenzamine increases peripheral blood flow in normotensive or hypertensive humans[8]. Oral doses of about 2 mg./kg. produce complete adrenergic blockade. In hypertension, it has effectively controlled blood pressure in about half of the patients treated. However, general use is limited by the large doses required, which often produce undesirable effects of adrenergic blockade, such as tachycardia, severe nasal stuffiness and orthostatic hypotension[2,8,14]. By combin-

ing these three agents, it was hoped that the hypotensive properties of each would be reinforced while the undesirable effects would be counteracted. Thus the undesirable tachycardia produced by Dibenzyline, for example, might be countered by the bradycardia produced by protoveratrine and Rauwolfia.

**Materials and Method.** Sixty-five patients seen at the Harrisburg Clinic comprised the clinical material of this study. This is not a free clinic. All of these patients had been known to us for a year or longer before this study was instituted. We feel, therefore, that the reactions and response of these patients are typical of the private patient and hence more directly applicable to the conditions of private medical practice than data obtained with patients seen in hospital outpatient departments. All patients selected for study had systolic blood pressures in excess of 150 mm. Hg, or diastolic pressure in excess of 100 mm. Hg, or both. Pertinent historical data on these patients are summarized in Table 1. Each patient was evaluated by blood pressure readings, physical examination, and a series of laboratory tests including an electrocardiogram, chest film, routine blood and urinalyses, and renal function tests including blood urea nitrogen, phenolsulfonphthalein test, and the Fishberg urine concentration test. Eye grounds of all of the patients were evaluated by a single individual before and after treatment. To facilitate comparison with previously reported studies of hypotensive therapy, we adopted the relatively strict criteria of Duncan[4] for classifying the response to treatment. Our classification of initial severity of hypertension was based primarily on the level of diastolic blood pressure. The classifications were cross-checked with the results of the laboratory tests. In the patients studied, we found diastolic pressure readings to be simpler and equally reliable to more complex systems which attempt to take laboratory measurements into account as well. In brief, severity was rated as *mild*, when initial *diastolic* blood pressure was 110 mm. or less, *moderate*, when initial *diastolic* blood pressure was from 111 to 130 mm., and *severe*, when initial *diastolic* pressure was 131 mm. or higher. Response was classified as *good*, a drop of 15 mm. or more in *diastolic* blood pressure to a final value of 100 mm. or less, or *fair*, a drop of 15 mm. or more in *diastolic* pressure but not to 100 mm. or less, or a *diastolic* drop of 10 to 15 mm. to 100 mm. or less, or *poor*, all other responses.

The rigidity of these criteria naturally tends to make some responses seem less satisfactory than they would seem in actual practice. For example, a patient whose initial reading was 200/140 would be considered only a "fair" response if the final reading was 130/105. Nevertheless, we feel that diastolic blood pressure is the simplest and most reliable indication of degree of hypertension and that a genuinely "good" result cannot be claimed unless the patient can be brought within normotensive limits.

TABLE 1.—CLINICAL DATA IN 65 HYPERTENSIVE PATIENTS TREATED WITH A COMBINATION OF DRUGS

| *Classification* | *Number of Patients* |
|---|---|
| AGE | |
| 20 to 39 | 3 |
| 40 to 59 | 36 |
| 60 and over | 26 |
| SEX | |
| Male | 25 |
| Female | 40 |
| SEVERITY | |
| Mild (diastolic BP under 110) | 14 |
| Moderate (diastolic BP 111–130) | 35 |
| Severe (diastolic BP over 130) | 16 |
| EVIDENCE OF RENAL DAMAGE | |
| With | 31 |
| Without | 34 |
| DURATION OF TREATMENT | |
| 1 to 3 months | 12 |
| 4 to 7 months | 17 |
| 8 months or more | 36 |

Dosage varied considerably among the patients. A summary of initial and maximum doses is presented graphically in Fig. 2. As shown, by far the most frequent dosage was 8 capsules of Formula B, a total daily dose of 100 mg. Rauwolfia, 0.8 mg. protoveratrine, and 20 mg. phenoxybenzamine (this, of course, was administered as 4 capsules of the double strength Formula A). With a number of patients an attempt was made to establish a maintenance dosage, once blood pressure had returned to a satisfactory level. Since many of our patients are still on full therapy, however, the figures for final maintenance doses are not as yet complete and have accordingly been omitted from Fig. 2.

Duration of treatment ranged from one month to approximately a year. We do not consider data complete on patients treated less than 6 months. However, we feel that an arbitrary exclusion of the data on the 13 patients treated for a shorter period would produce an inaccurate picture of the over-all results obtained.

Prior to this study, most of the patients had undergone at least one additional hypotensive regimen. Results of previous therapy are summaried in Table 2. Where response to previous treatment was known, the drugs involved were sometimes continued during the study. Sedation, for example, was continued in a number of patients. Six patients took reserpine and one took hydralazine followed by the addition of the combination Rauwolfia-protoveratrine-phenoxybenzamine capsules. In no case could the results reported be attributed to concomitant therapy alone.

**Results.** Table 3 contains a summary of responses obtained in terms of initial severity, duration of treatment, and dosage. In all, 51 of the 65 patients studied (78.5%) experienced a drop in diastolic pressure of at least 10 mm. All of those obtaining "good" results (57% of the total group) and about one-third of those obtaining "fair" results were normotensive by the end of the study. Probably the most dramatic single result was achieved in the case described below:

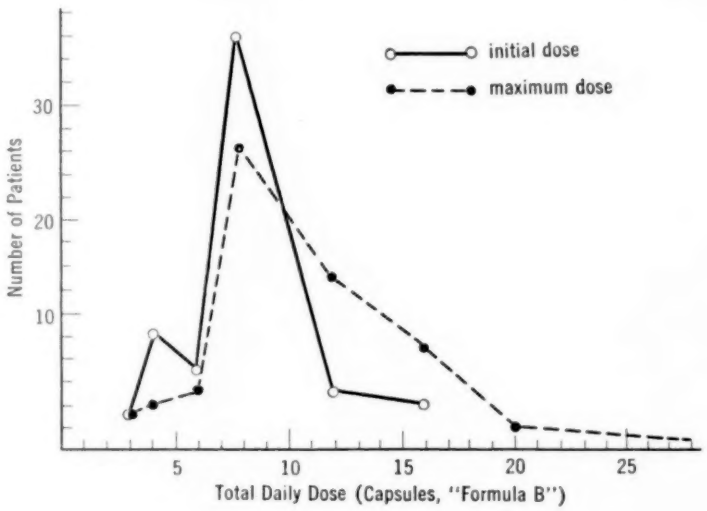


Fig. 2.—Dosage range.

TABLE 2.—RESPONSE TO PREVIOUS THERAPY

| | *Good* | *Fair* | *Poor* | *Total* |
|---|---|---|---|---|
| Hexamethonium | | 1 | 1 | 2 |
| Hydralazine | 1 | 2 | 8 | 11 |
| Veratrum | 1 | 6 | 11 | 18 |
| Rauwolfia | | 2 | 6 | 8 |
| Nitrates | | | 9 | 9 |
| Thiocyanates | 1 | 2 | 6 | 9 |
| Sedatives | 1 | 22 | 13 | 36 |
| Low-salt Diet | 55 | 13 | 14 | 32 |
| Sympathectomy | | 1 | 1 | 2 |
| Totals | 9 | 49 | 69 | 127 |

**Case Report.** CASE 1. G. B., a 50-year-old white male. At the beginning of the study, examination revealed a sitting blood pressure of 250/160 mm. which had been known to exist for 5 years. The patient had had repeated renal calculi with infection. His left kidney was practically nonfunctioning. Eye grounds were Grade II. Physical examination revealed an enlarged heart and a Grade II systolic murmur at apex and base. On chest film the heart/chest ratio was found to be

16.4/32.6. The electrocardiogram showed myocardial damage with posterolateral ischemia and peaked "T" waves in leads $V_2$, $V_3$, $V_4$ and inverted "T" waves in $V_6$ and AVF. Blood count and urinalysis were normal except for presence of albuminuria. Total dye excretion in 2 hours of the intravenous phenolsulfonphthalein test was 45%. Blood urea nitrogen was 18.5 mg. per 100 cc. The patient reported dyspnea and palpitations and angina on exertion. He had been digitalized and $V_4$ and upright waves in $V_6$ and AVF; blood urea nitrogen, 14.4 mg. per 100 cc.; phenolsulfonphthalein (2-hour dye excretion) 63.5%; blood count and urinalysis, normal.

It will be noted in Fig. 3 that the systolic pressure had apparently begun to rise again after the minimum reading recorded at 12 weeks. The upward trend was not continued and blood pressure readings taken 2 months after the last recorded on the graph had not increased over the last reading shown.

TABLE 3.—SUMMARY OF RESULTS OF COMBINED DRUG TREATMENT IN 65 HYPERTENSIVE PATIENTS

| | *Response* | | | |
|---|---|---|---|---|
| *Correlation* | *Good* | *Fair* | *Poor* | *Total* |
| vs. Initial severity | | | | |
| Mild | 7 | 4 | 3 | 14 |
| Moderate | 23 | 7 | 5 | 35 |
| Severe | 7 | 4 | 5 | 16 |
| vs. Duration of treatment | | | | |
| 1 to 3 months | 5 | 2 | 3 | 10 |
| 4 to 7 months | 9 | 2 | 8 | 19 |
| 8 month or more | 23 | 10 | 3 | 36 |
| vs. Maximum dose in patients studied 6 months or more | | | | |
| 2 A | 1 | 1 | | 2 |
| 3 A | 1 | | 1 | 2 |
| 4 A | 14 | 4 | 3 | 21 |
| 6 A | 9 | 2 | 3 | 14 |
| 8 A | 5 | 4 | 1 | 10 |
| 10 A | 1 | | | 1 |
| 16 A | 1 | 1 | | 2 |
| Over-all results (all patients) | 37 | 14 | 14 | 65 |
| Per cent | 57 | 21.5 | 21.5 | 100 |
| Over-all results (in all patients studied 6 months or more) | 32 | 12 | 7 | 52 |
| Per cent | 61.5 | 23 | 13.5 | 80 |

for approximately one year. In addition he had been treated (with indifferent results) with veratrum viride, sedatives, and low salt diet. He was started at the relatively high dosage of 8 capsules of Formula A. Since no disturbing side effects developed, he was continued at this dosage throughout the treatment. Blood pressure response for this patient is shown in Fig. 3. At 6, 7, and 8 months, the sitting blood pressure was 176/96. No change was noted in the eye grounds. All tests were repeated at 6 months and the following results were reported: heart/chest ratio, 15.1/32.6; electrocardiogram, slight general improvement with lowered "T" waves in $V_2$, $V_3$,

Although this response was, in many ways, the best encountered, it was by no means an exception. Decreases of from 30 to 50 mm. in diastolic pressure were frequent, as were proportionately larger decreases in systolic pressure.

As shown in Table 1, 14 patients had a mild degree of hypertension at the beginning of treatment. Although the percentage of good responses in this group (50%) is not as impressive as in the group with moderately severe hy-

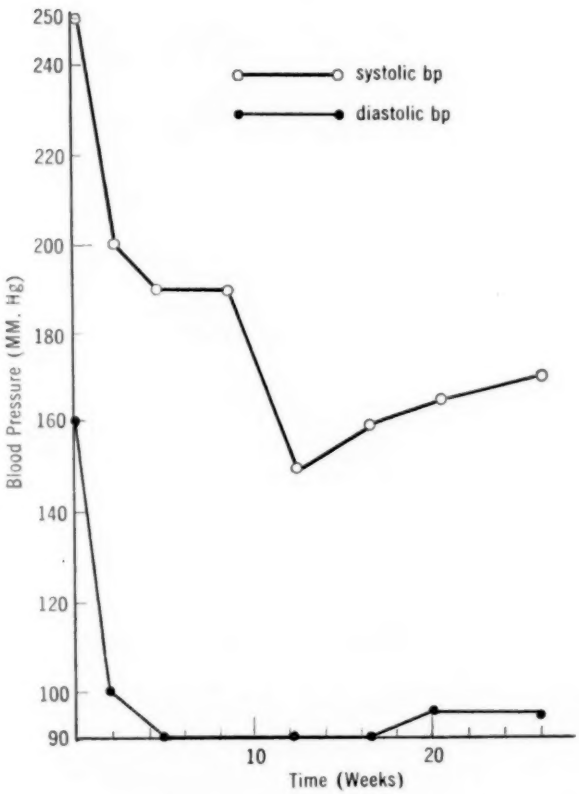


Fig. 3.—Blood pressure response (patient G. B.).

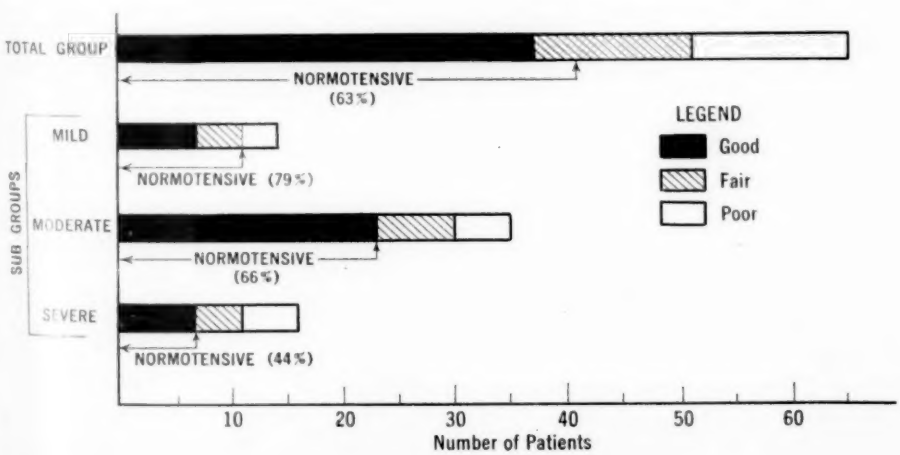


Fig. 4.—Summary of results.

pertension (66%), the practical clinical fact that 79% of the mild hypertensives become normotensive should be stressed. A graphical presentation of results (Fig. 4) illustrates the correlation between good results expressed as a function of diastolic blood pressure lowering and in terms of ultimate aim of therapy: to make the hypertensive patient normotensive.

A statistical analysis of laboratory findings showed the decrease in blood urea nitrogen to be significant*. This response has been graphed in Fig. 5. Changes in other tests were not statistically significant (Table 4). Results obtained with the Fishberg test were, we feel, equivocal. Although no significant changes were observed, our impression was that outpatients normally are not observed closely enough to make readings obtained with this test reliable.

Side effects were sufficiently severe to cause 7 patients to discontinue therapy. In view of the potency of the

TABLE 4.—ANALYSIS OF LABORATORY FINDINGS IN 65 HYPERTENSIVE PATIENTS GIVEN COMBINED DRUG TREATMENT

| | *Number of Observations* | *Average Difference* | *Standard Error of Difference* | *Students "t" for Average Difference* + | 0 | *Significant* |
|---|---|---|---|---|---|---|
| Chest Film | 43 | — .11 | 0.692 | | 1.06 | no |
| PSP | 45 | −2.14 | 15.148 | | 1.00 | no |
| BUN | 43 | −2.27 | | (see Fig. 5) | | yes |
| Fishberg | 38 | −1.42. | 4.841. | | 1.81. | no |
| | | 1.26 | 5.500 | | 1.41 | |

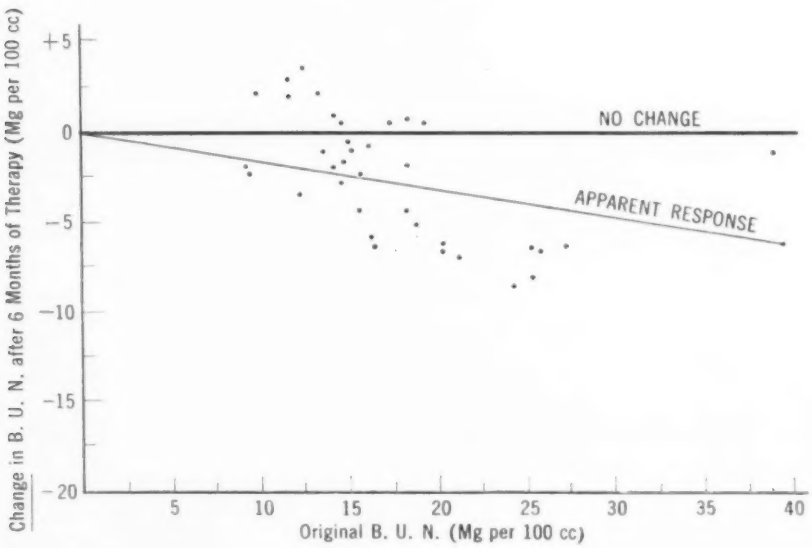


Fig. 5.—Apparent response in B. U. N. values in patients.

*P value equals 0.001.

medication, this is a remarkably small percentage of the total group (10.8%), particularly so, when one considers that these were ambulant private patients who had no compunctions about demanding a change in regimen if they considered the side effect too odious. This is not to imply that side effects did not cause complaints or that their incidence was not appreciable. As shown in Table 5, there was a total of 70 reports of side effects. The most prevalent and distressing complaint was a feeling described variously as "weakness," "fatigue," "all-gone feeling," and the like. Thirty-six patients reported this reaction. The symptom was not controlled in 14 of these patients and in 4 of them it was sufficiently severe to require that the treatment be changed. Toward the end of the study we began using d-amphetamine sulfate in an attempt to control the symptom and, although too few patients have received the drug to permit final conclusions, the results were definitely encouraging. Of approximately 10 patients who received amphetamine, six reported a definite abatement of the side effect and in none of these patients did the drug appear to decrease the effectiveness of the hypotensive preparation. Since the feeling of "fatigue" was the most troublesome side effect encountered, we feel adjunctive use of amphetamines may prove particularly valuable.

The second most prevalent side effect was nasal stuffiness. This occurred in 24 patients and required a discontinuance of therapy in two. Since these two patients also experienced the feeling of fatigue described above, it is possible that the stuffiness alone might not have caused them to stop treatment. This, however, is merely conjecture.

A third side effect probably attributable to the phenoxybenzamine, was an absence of semen reported in 8 of the 25 males under therapy. Loss of libido did not accompany the loss of semen and, although the ejaculation itself was absent, orgasm was not. When the possibility of this side effect was not previously explained to the patients experiencing it, it proved most disturbing. However, adequate warning did much to alleviate the patients' concern and the one patient who reported this side effect and also discontinued therapy did so because of the side effects of fatigue and nasal stuffiness also reported, rather than because of the loss of ejaculatory fluid.

It is notable that neither nausea and vomiting nor orthostatic hypotension, the most distressing side effects of protoveratrine and phenoxybenzamine respectively, occurred when the two drugs were administered in this combination.

As mentioned above, the total number of patients not followed for 6 months or more was 13. Of these, one

TABLE 5.—DESCRIPTION OF SIDE EFFECTS FROM COMBINED DRUG TREATMENT

| *Side Effect* | *Total Number of Reports* | *Controlled by Reducing Dose* | *Controlled by Chlortrimeton or Dexedrine* | *Mild but Not Control.* | *Mod. Uncon-trol.* | *Severe Uncon-trolled* |
|---|---|---|---|---|---|---|
| Nasal Stuffiness | 24 | 6 | 9 | 2 | 5 | 2 |
| Weakness, fatigue | 36 | 16 | 6 | 4 | 6 | 4 |
| Loss of semen | 8 | | | | 7 | 1 |
| Palpitation | 1 | 1 | | | | |
| Weight Gain | 1 | | | 1 | | |

patient died 3 months after treatment was begun. Death was attributed to metastatic carcinoma of the breast. The patient (A.H.) also suffered from severe hypertension. Her initial blood pressure was 234/132 mm. and renal function studies showed definite evidence of renal damage. The blood pressure response at 3 months was classified as "good," the last reading taken being 198/100 mm.

The 7 patients who stopped because of side effects and 5 who were merely added late in the study comprise the remainder of the group treated less than 6 months. Responses in the 5 patients added late were classified as "good" in 3 and "fair" in 2.

It should be mentioned that maintenance therapy was attempted once the patients achieved a satisfactory blood pressure response. Although this phase of the investigation is still continuing and final conclusions cannot be drawn, our preliminary experience is that the average patient can be satisfactorily maintained on a daily dose of from 4 to 8 capsules of Formula B.

Thirty-five patients were taken from a satisfactory blood pressure level on "DRP" therapy and placed on placebo capsules. After 2 weeks' observation the average rise in systolic pressure in these patients was 34.22 and the average rise in diastolic pressure was 21.26. The patient in this group showing the least change had a blood pressure of 156/98 on "DRP" and 164/100 on placebo. The patient showing the greatest change had a pressure of 150/100 on "DRP" and 246/140 on placebo. The placebo used was identical in all respects except for active ingredients and was substituted without the patients' knowledge. Reinstatement of "DRP" therapy again controlled the blood pressure in all 35 cases.

As a final note on combination therapy, it deserves mention that one patient (R.W.), although classified as a poor result, did actually achieve a satisfactory response when hydralazine was added to the regimen. Dosage in this patient consisted of four capsules of Formula A plus 200 to 300 mg. of hydralazine per day.

**Discussion.** In evaluating the overall worth of any regimen, results alone tell only part of the story. The reason behind the results is no less important. In terms of results alone, it will be seen that a poor response was encountered in 14 patients. This constitutes 21.6% of the study group and, when compared with results obtained with a number of other hypotensive regimens, is relatively small. An examination of the reasons behind the failures is also illuminating. In 7 of the 14, side effects were relatively severe and 6 of these 7 discontinued therapy. The seventh, perhaps more hardy than the rest, not only continued therapy but actually allowed hydralazine to be added to the regimen. After some time the side effects diminished in intensity and this patient eventually achieved a good response. This raises the question of whether the 6 who stopped treatment might not have attained good results had they continued somewhat longer. Only 7 patients treated 6 months or longer were classified as poor responses. Thus it seems likely that longer treatment might have produced better results. Since side effects are the limiting factor with most potent drugs, whether used singly or in combination, it would normally seem pointless to wonder at possibly better results that might have been obtained but for these unwanted symptoms. However, although efforts to counter side effects were inadequate in these patients there is reason to hope that improvement would have been possible. Our finding that nasal stuffiness could often be relieved by antihistaminic agents and that fatigue

could be alleviated by d-amphetamine sulfate (Dexedrine) might well have been applied to advantage with these patients had we known in time.

Disregarding what might have been, however, this study revealed that the regimen was capable of producing a normotensive blood pressure level in 63% of the patients studied. Although an appreciable response occurred in the severely hypertensive patients treated, the most satisfactory results were produced with mild or moderately severe hypertension. Of patients falling in these categories, nearly 70% became normotensive, and good responses by the criteria stated were achieved in 61.5%. An additional 22% obtained fair responses. The statistics show that approximately 80% of the 65 patients were appreciably helped by the regimen and only 11% experienced prohibitive side effects. In our experience, these results are outstanding.

The response to this multiple regimen adds further confirmation to the premise that hypertension must be regarded less as a clinical entity than as a syndrome with multiple etiological factors. Because the etiology itself is probably a combination of causes, a combination of therapeutic agents would seem the best means of combating the condition. Polytherapy is not only indicated, it seems essential in the majority of patients.

Based on our experience, we presently consider this combination of Rauwolfia, protoveratrine, and phenoxybenzamine as the preparation of first choice in all hypertensive patients requiring treatment except those few whose condition is clearly attributable to a specific pathological process.

**Summary.** 1. Sixty-five patients with hypertension classified as mild in 14, moderate in 35, and severe in 16 were treated with a hypotensive preparation (Mio Pressin) consisting of Rauwolfia, protoveratrine, and phenoxybenzamine combined in fixed proportions.

2. Good results were obtained in 37 patients, fair results in 14, and poor results in 14. Sixty-three per cent of the patients had become normotensive by the conclusion of the study.

3. Side effects consisted of nasal stuffiness (24 times), fatigue (36 times), loss of semen (8 times), and one each of palpitation and weight increase.

4. Severity of side effects was usually mild and required discontinuance of therapy in only 7 of the patients treated. The most prevalent side effects, nasal stuffiness and fatigue, could usually be controlled by using antihistamines for the former and d-amphetamine sulfate for the latter. The use of amphetamines as adjuvant therapy had no adverse effect on the blood pressure response.

5. Based on the experience reported, the combination of agents studied is felt presently to be the hypotensive preparation of choice, wherever the hypertension may be inferred to be the result of complex or obscure processes rather than a specific etiological factor.

## REFERENCES

1. **Alexander, W. M., Richards, A. B.,** and **Abreu, B. E.:** Fed. Proc., **12,** 297, 1953.
2. **Bakke, J. L.,** and **Williams, R. H.:** Am. J. Med., **14,** 141, 1953.
3. **Currens, J. H., Myers, G. S.,** and **White, P. D.:** Am. Heart J., **46,** 576, 1943.
4. **Duncan, G. G.:** New England J. Med., **249,** 85, 1953.
5. Editorial: Ann. Int. Med., **38,** 142, 1953.
6. **Fellows, E. J., McLean, R. A., Macko, E., Kerwin, J. F., Hall, G. C., Milnes, F. J., Witt, I. H.,** and **Ullyot, G. E.:** J. Pharmacol. & Exper. Therap., **110,** 463, 1954.
7. **Fries, E. D.:** Med. Clin. N. America, **38,** 363, 1954.

8. **Haimovici, H.:** Angiology, **2**, 531, 1951.
9. **Hoobler, S. W., Cooley, R. W., Kabza, T. G.,** and **Loyke, H. F.:** Ann. Int. Med., **37**, 465, 1952.
10. **Meilman, E.,** and **Krayer, O.:** Circulation, **1**, 204, 1950.
11. Iidem: Ibid., **6**, 212, 1952.
12. **Moe, G. K.,** and **Mendez R.:** J. Pharmacol. & Exper. Therap., **82**, 167, 1944.
13. **Moser, M., Watkins, D., Morris, N., Prandoni, A. G.,** and **Mattingly, T. W.:** Circulation, **8**, 224, 1953.
14. **Moser, M., Walters, M., Master, A. M., Taymor, R. C.,** and **Metraux, J.:** A.M.A. Arch. Int. Med., **89**, 708, 1952.
15. **Wilkins, R. W.:** Med. Clin. N. America, **37**, 1303, 1953.
16. Idem: Ann. Int. Med., **37**, 1144 1952.
17. **Wilkins, R. W.,** and **Judson, W. E.:** New England J. Med., **248**, 48, 1953.
18. **Wilkins, R. W., Judson, W. E., Stone, R. W., Hollander, W., Huckabee, W. E.,** and **Friedman, I. H.:** New England J. Med., **250**, 477, 1954.

## SUMMARIO IN INTERLINGUA

### Experientias Clinic con un Nove Combination de Agentes Hypotensive

1. Un preparato hypotensive (Mio Pressin), consistente de Rauwolfia, protoveratrina, e phenoxybenzamina in fixe proportiones, esseva usate in le tractamento de 65 patientes hypertensive. Le gruppo total includeva 14 casos classificate como leve, 35 classificate como moderate, e 16 classificate como sever.

2. Le resultatos obtenite esseva bon in 37 patientes, satisfacente in 14, e magre in 14. Al fin del presente studio, 63 pro cento del patientes habeva devenite normotensive.

3. Le effectos lateral consisteva in constipation nasal (24 occurrentias), fatiga (36), perdita de semine (8), palpitation (1), e augmento de peso (1).

4. In general le severitate del effectos lateral esseva pauco pronunciate. Illo necessitava un interruption del tractamento in solmente 7 casos. Le plus frequente effectos lateral, *i.e.* constipation nasal e fatiga, esseva generalmente tractabile per le administration de antihistaminas in le casos del prime e de sulfato de d-amphetamina in le casos del secunde. Le uso auxilio-therapeutic de amphetaminas non influeva maleficamente super le pression del sanguine.

5. Super le base del experientias hic reportate nos opina que al tempore presente le combination de agentes hypotensive usate in nostre studio es le preparato de selection in omne casos in que on pote supponer que le hypertension es le resultato de complexe o obscur processos plus tosto que de un specific factor etiologic.

# THE EFFECTS OF HIGH CHOLESTEROL DIET ALONE AND PLUS CORTISONE ADMINISTRATION ON PHOSPHOLIPID TURNOVER AND LIPID PARTITION IN PLASMA, LIVER, AND AORTA OF RABBITS

By Abraham Dury, Ph.D.
DIRECTOR OF RESEARCH

(From The Dorn Laboratory for Medical Research, Bradford Hospital, Bradford, Pennsylvania)

Since Anitschkow and Chalatow[1] experimentally induced atherosclerosis in rabbits furnished a cholesterol-supplemented diet it was believed that there was a close relationship between high blood cholesterol levels and the pathogenesis of atherosclerosis. In fact, a good correlation had been reported[4] between the serum cholesterol level and the severity of atherosclerosis in rabbits given a high cholesterol diet. It is known also that a hyperphospholipidemia occurs in cholesterol-fed rabbits; but the change in concentration of this lipid fraction is relatively less than the elevation in plasma cholesterol. Recently, retardation of lipid deposition in the intima of the aorta was reported in alloxan-injected[3,5], and cortisone-injected[12,14], cholesterol-fed rabbits although the cholesterolemia in these animals was greater than in the rabbits fed only a high cholesterol diet. Since the plasma cholesterol-phospholipid ratio was not different in the control and experimental animals, it appeared unlikely to these investigators that this mechanism, *per se*, was responsible for the retardation of the development of atherosclerosis. On the other hand, Gordon, *et al.*[10] reported that in their cortisone-treated, cholesterol-fed rabbits the plasma cholesterol-phospholipid ratio was "more normal" and suggested this might explain (as one of several other possibilities) the decreased severity of atherosclerosis observed in their experimental rabbits.

The above-mentioned results in alloxan-injected, and cortisone-injected, cholesterol-fed rabbits indicated that a general alteration in the lipid-metabolic state of the organism rather than an alteration in a specific plasma lipid component or interrelationship might be of considerable influence in the development of atherosclerosis. Therefore, in the present experiment the lipid partition and the turnover of phospholipids in plasma, liver and aorta were determined in rabbits subjected to a high cholesterol diet without and with cortisone exhibition.

**Materials and Methods.** New Zealand white female rabbits of pedigreed stock were employed in the following groups: (A) 7 rabbits provided with a high cholesterol diet, and daily injections of physiological saline; (B) 8 rabbits given a control diet, and daily saline injections; (C) 6 rabbits given a high cholesterol diet, and daily injections of cortisone. Cholesterol was administered by coating 100 gm. of commercial rabbit food pellets with 1 gm. of cholesterol (Merck)* dissolved in 2.8 gm. of vegetable fat (Crisco). The control diet was prepared in the same manner with only the vegetable fat added. The diets were prepared in 10 kg. batches at regular intervals. Each rabbit was furnished 100 gm. of diet per day and tap water *ad libitum*. All of the food was consumed each day. Rabbits of Group C were injected intramuscularly with 10 mg. of cortisone acetate (in saline) daily; rabbits of Groups A and B were injected intramuscularly with 0.4 cc. saline. The duration of

*We wish to thank Frederick K. Heath, M.D. for the generous supply of cholesterol (Cholesterin, U.S.P.; Merck).

the dietary and injection regimes was 35 days.

On the final day of the experiment 0.5 millicurie of radioactive phosphate ($P^{32}$) was administered intravenously to control and experimental animals. Heart blood was obtained from all animals at 6 hours and from some animals in each group at 2 and 4 hours after $P^{32}$ administration. After the blood sample was secured at the 6-hour interval, an overdose of Evipal was injected by vein and the liver and all of the aorta then were removed. The aorta was examined macroscopically for evidence of atheromata, and a uniform section of the ascending aorta was cut off and fixed in formalin for subsequent microscopic examination. The severity of atherosclerosis was graded from 0 (normal) to 4 plus (severe) on the basis of the histological observations. The remainder of the cleaned aorta, a specimen section of the liver, and aliquot of the plasma were used for the various chemical and radioactive determinations.

The lipids of plasma, liver, and aorta were extracted with hot alcohol-ethyl ether. The extracts were collected and taken almost to dryness *in vacuo*. The residue then was redissolved in petroleum ether and made to a convenient volume from which suitable aliquots were taken for the chemical and radioactive determinations. Details of the procedures used in this laboratory for determinations of lipid components were the same as previously described[7,8]. Total lipid was calculated from weight of residue after evaporation of the petroleum ether and drying to a constant weight. Lipid phosphorous determined by the methods of Youngsburg and Youngsburg[16] and Fiske and SubbaRow[9]; and phospholipid values were calculated from the lipid-P values × 26. Total and free cholesterol determined by the method of Schoenheimer and Sperry[13] and ester cholesterol by difference. The neutral fat was calculated by subtracting the sum of the values of the phospholipid, free cholesterol and cholesterol oleate from the total lipid value. Plasma glucose was determined by the photometric method of Nelson[11]. Separate liver specimens were homogenized in 10% trichloracetic acid for the determination of inorganic and organic acid-soluble phosphates in liver. The inorganic and organic fractions were separated by precipitation with magnesium[17] and after centrifugation determinations for $P^{31}$ and $P^{32}$ were done on the supernatant and dissolved precipitate.

**Results.** BIOCHEMICAL FINDINGS. *High Cholesterol Diet.* The average concentrations of the various lipid fractions in plasma, liver, and aorta of the three groups of rabbits are shown in Parts A, of Tables 1 to 3. Statistical analysis of the data showed that all lipid fractions of the plasma except neutral fat were significantly higher in the cholesterol-fed, saline-injected animals (Group B) compared with controls (Group A). With regard to the liver lipids, the concentrations of total lipids, and total, free and esterified cholesterol in Group B were significantly elevated while the phospholipid concentration was significantly less than the controls. Inspection of the data relating the aorta lipid partition shows that the concentrations of total and esterified cholesterol in the cholesterol-fed, saline-injected group were significantly elevated while the concentrations of all the other lipid fractions were not deviate from the respective control values.

*High Cholesterol Diet plus Cortisone.* The influence of daily cortisone administration on the lipid fractions of plasma, liver, and aorta of cholesterol-fed rabbits (Group C) are shown also in Tables 1 to 3, Parts A. The neutral fat concentrations in plasma and liver of Group C rabbits were about five times greater than the respective mean values in the cholesterol-fed, saline-injected (Group B); but the cholesterol and phospholipid concentrations of liver and plasma were not different in these two groups. The concentrations of the various aortic lipid fractions in the cholesterol-fed, cortisone injected rabbits were statistically not different from the respective values in the cholesterol-fed group without cortisone exhibition.

The plasma glucose concentrations determined in the three groups of rabbits were not significantly different. The mean glucose values in Groups A,

TABLE 1.—LIPIDS PARTITION AND PHOSPHOLIPID TURNOVER IN PLASMA OF RABBITS PROVIDED WITH A CONTROL-TYPE DIET (A), A HIGH CHOLESTEROL DIET WITHOUT (B), AND WITH CORTISONE ADMINISTRATION (C)

Part A—Lipids Partition

TABLE 1.—LIPIDS PARTITION AND PHOSPHOLIPID TURNOVER IN PLASMA OF RABBITS PROVIDED WITH A CONTROL-TYPE DIET (A), A HIGH CHOLESTEROL DIET WITHOUT (B), AND WITH CORTISONE ADMINISTRATION (C)

Part A. Lipids Partition (mg./100 cc.)

| *Groups* | *Total lipids* | *Phospholipids* | *Total chol.* | *Free chol.* | *Ester chol.* | *Neutral fat* |
|---|---|---|---|---|---|---|
| A. (8) | 480.3 ± 80.9[1] | 150.8 ± 18.2 | 109.3 ± 24.5 | 31.6 ± 8.3 | 72.3 ± 16.4 | 172.9 ± 28.3 |
| B. (7) | 3164.6 ± 476.4#[4] | 576.4 ± 75.3# | 1439.9 ± 299.2# | 327.7 ± 61.3# | 1112.2 ± 238.6# | 351.7 ± 93.7 |
| C. (6) | 4788.3 ± 666.5 | 829.8 ± 118.1 | 1558.0 ± 322.5 | 355.3 ± 63.6 | 1202.7 ± 263.3 | 1677.8 ± 296.7# |

Part B. Concentrations and Specific Activities (S. A.) of Plasma acid-soluble Phosphate and Phospholipid 6 hours after intravenous $P^{32}$.

| | *PAS* | | *Phospholipid — P* | | |
|---|---|---|---|---|---|
| | *mg./100 cc.* | *S.A.*[2] | *mg./100 cc.* | *% I.D./cc.*[3] | *S. A.* |
| A. | 5.51 ± .31 | 115. ± 4.9 | 6.31 ± .84 | 2.46 ± .54 | 4.44 ± .26 |
| B. | 5.40 ± .19 | 157. ± 18.7 | 20.52 ± 3.24 | 9.11 ± 1.92# | 4.48 ± .67 |
| C. | 4.00 ± .38# | 207. ± 23.8 | 31.91 ± 4.54 | 20.41 ± 2.73# | 6.89 ± 1.21 |

See text for preparation of diets and cortisone injection dose.
[1]All values are Mean ± S. E. [2]Percentage of injected $P^{32}$ per milligram of phosphorus × $10^3$.
[3]Amount of radioactive phospholipid per cubic centimeter of plasma × $10^4$.
[4]Probability of differences between means of Groups A and B, and between Groups B and C occurring by chance alone are indicated by: ° for "P" = 0.05 — 0.01; and # for "P" = less than 0.01.

TABLE 2.—LIPIDS PARTITION AND PHOSPHOLIPID TURNOVER IN LIVER OF RABBITS PROVIDED WITH A CONTROL-TYPE DIET (A), A HIGH CHOLESTEROL DIET WITHOUT (B), AND WITH CORTISONE ADMINISTRATION (C).

Part A. Lipids Partitions (gm. %)

| *Groups* | *Total lipids* | *Phospholipids* | *Total chol.* | *Free chol.* | *Ester chol.* | *Neutral fat* |
|---|---|---|---|---|---|---|
| A. | 4.88 ± .14[1] | 3.71 ± .14 | .28 ± .025 | .22 ± .004 | .06 ± .02 | .84 ± .10 |
| B. | 5.90 ± .52°[2] | 3.06 ± .13# | 1.41 ± .23# | .31 ± .023# | 1.09 ± .28# | .86 ± .13 |
| C. | 8.46 ± .81° | 2.69 ± .36 | 1.34 ± .32 | .26 ± .042 | 1.09 ± .29 | 3.93 ± .62# |

Part B. Concentrations and Specific Activities (S. A.) acid-soluble Phosphate and Phospholipid in Liver 6 hours after Intravenous $P^{32}$

| | *IAS* | | *OAS* | | *Phospholipid — P* | | |
|---|---|---|---|---|---|---|---|
| | *mg./100 cc.* | *S.A.* | *mg./100 cc.* | *S.A.* | *mg./100 cc.* | *S.A.* | *Liver Wt. gm.* |
| A. | 25.4 ± .9 | 118. ± 9.4 | 115.0 ± 9.1 | 48. ± 3.3 | 1.35 ± .07 | 10.28 ± .99 | 84. ± 16.6 |
| B. | 20.8 ± 1.1# | 139. ± 12.2 | 98.2 ± 5.0 | 72. ± 8.4° | 1.16 ± .07 | 17.92 ± 1.91# | 97. ± 7.1 |
| C. | 18.1 ± 4.5 | 196. ± 14.3# | 92.8 ± 12.2 | 101. ± 9.0° | 1.03 ± .14 | 26.43 ± 4.83 | 117. ± 18.4 |

See legend Table 1 for explanation of signs and abbreviations.
[1]All values are Mean ± S. E. [2]Differences between means of Groups A and B, and B and C were tested for statistical significance.

B, and C were 141, 133, and 140 mg. per 100 cc., respectively.

*Phospholipid Turnover.* The average specific activities of acid-soluble plasma phosphate at 2, 4, and 6 hours after $P^{32}$ administration are presented in Fig. 1 as a semilog plot. The specific activities of Groups A and B, and B and C were not significantly different. Therefore, the experimental conditions apparently had no effect on the turnover of plasma acid-soluble phosphates, and the latter probably was not a factor in the phospholipid turnovers in the tissues which were studied.

The specific activities of plasma, liver, and aorta phospholipid, and liver inorganic and organic acid-soluble phos-

TABLE 3.—LIPIDS PARTITION AND PHOSPHOLIPID TURNOVER IN AORTA OF RABBITS PROVIDED WITH A CONTROL-TYPE DIET (A), A HIGH CHOLESTEROL DIET (B) CHOLESTEROL DIET PLUS CORTISONE ADMINISTRATION (C).

| *Constituents* | *Groups* A | B | C |
|---|---|---|---|
| | Part A. Lipids Partition (Gm. %) | | |
| Total lipids | 10.25 ± 1.68[1] | 10.84 ± 1.39 | 11.98 ± .94 |
| Phospholipids | .91 ± .027 | .93 ± .05 | .98 ± .08 |
| Total chol. | .16 ± .007 | .29 ± .016#[2] | .30 ± .041 |
| Free chol. | .13 ± .006 | .16 ± .016 | .19 ± .021 |
| Ester chol. | .02 ± .005 | .13 ± .02# | .12 ± .029 |
| Neutral fat | 9.17 ± 1.83 | 9.53 ± 1.37 | 10.62 ± 1.02 |
| | Part B. Concentrations and Specific Activities (S. A.) of Aorta Phospholipid 6 hours after Intravenous $P^{32}$. | | |
| Lipid-P mg./100 cc. | 35.0 ± 1.5 | 36.8 ± 2.3 | 37.7 ± 3.1 |
| S. A. | 6.13 ± .90 | 5.77 ± 1.08 | 7.24 ± 1.07 |

See legend Table 1 for explanation of signs and abbreviations.

[1]All values are Mean ± S. E. [2]Differences between means of Groups A and B, and B and C were tested for statistical significance.

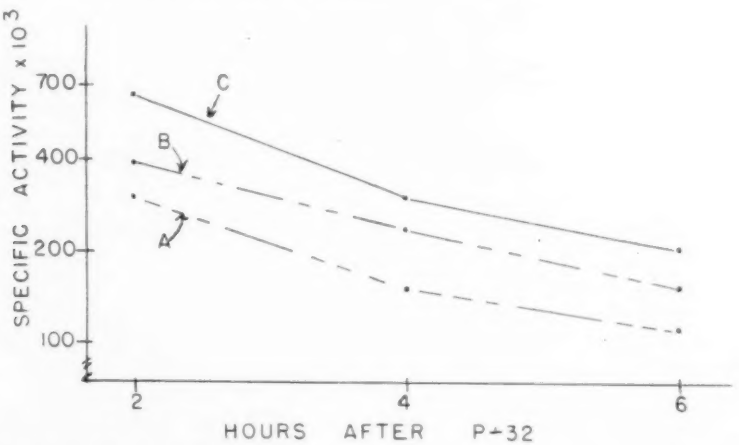


Fig. 1.—Semi-logarithmic plot of the plasma acid-soluble phosphate specific activities against time in: rabbits fed a control-type diet (*A*); a cholesterol-supplemented diet (*B*); and a cholesterol-supplemented diet plus daily cortisone administration, intramuscularly. The points on the curves are the means of each group.

phate are shown in Parts B, of Tables 1 to 3. The specific activities were calculated as the percentage of administered $P^{32}$ in the phospholipid fraction per milligram of phospholipid-phosphorus, or the percentage of $P^{32}$ in the acid-soluble inorganic and organic phosphate per milligram of phosphorus. The plasma phospholipid specific activity (Table 1) of the cholesterol-fed, saline-injected rabbits (Group B) was not statistically different from the controls (Group A). These data, however, do not adequately show the greatly increased turnover of plasma phospholipid which occurred in the rabbits of Group B injected, cholesterol-fed animals (Group B) showed that the amount of radioactive phospholipid per cubic centimeter of plasma in the former group was significantly greater (Part B, Table 1). Inspection of the data in Tables 2 and 3, Parts B, however, show that the specific activities of liver and aorta phospholipids in these two groups were not significantly different.

In Table 4 are shown the interrelationships of some plasma lipids of the three groups of this study. It is evident from these data that the concentrations of plasma-free cholesterol and phospholipid in the rabbits of Group

TABLE 4.—EFFECT OF HIGH CHOLESTEROL DIET WITHOUT AND WITH CORTISONE ADMINISTRATION ON PLASMA LIPID INTERRELATIONSHIPS IN RABBITS

| *Groups* | *F. C./T. C.*[1] *× 100* | *T. C./Plp. × 100* | *N. F./Plp.* |
|---|---|---|---|
| Control diet (A) | 29.6 ± 1.3[2] | 63.7 ± 7.7 | 1.13 ± .08 |
| Cholest. diet (B) | 23.4 ± 0.7#[3] | 237.4 ± 26.6# | .78 ± .13° |
| Cholest. diet and Cortisone (C) | 24.0 ± 1.5 | 192.8 ± 29.1 | 2.11 ± .40# |

[1]Abbreviations: F. C. = free cholesterol; T. C. = total cholesterol; Plp. = phospholipid; N. F. = neutral fat.

[2]All values are Mean ± S. E.

[3]Probability of differences between means of Groups A and B, and between Groups B and C occurring by chance alone are indicated by: ° for "P" = 0.05 — 0.01; # for "P" = less than 0.01.

since the concentration of plasma phospholipid in these animals was three times greater than in the controls. The data in Table 1 show that the amount of radioactive phospholipid per cubic centimeter of plasma was 400% greater in the rabbits of Group B compared with the control group. The liver phospholipid specific activity (Table 2) was significantly increased also in the former group. However, the aortic phospholipid specific activity was not statistically different in the two groups (Table 3).

A comparison of the isotopic data of the cortisone-injected, cholesterol-fed rabbits (Group C) with the saline-B were elevated much less relative to the increase in total cholesterol, while the concentration of the neutral fat fraction was relatively depressed compared to the change in phospholipid concentration. On the other hand, in the cortisone-injected, cholesterol-fed rabbits the major alteration in plasma lipid interrelationships apparently was a marked increase in the neutral fat content relative to the phospholipid concentration.

HISTOLOGIC OBSERVATIONS. Macroscopic atheromata were not observed in the aorta of any of the rabbits of the three groups. Histologic examina-

tion* of sections of the ascending aorta revealed in the cholesterol-fed rabbits, without and with cortisone, one case in each group of a medial degenerative change classified as of one plus severity.

**Discussion.** The cholesterol-supplemented diet was purposefully provided to the rabbits in this study for approximately one-half the usual period employed to induce atheromata experimentally in cholesterol-fed rabbits. In the present study, the increase in plasma cholesterol concentration within one month was comparable in extent to that found in rabbits on a high cholesterol diet for much longer periods of time[10,14]. Furthermore, evidence also was presented that the liver cholesterol content in these rabbits also was profoundly increased (500%). The concentration of aorta cholesterol also was increased; but the change, although significant, was not remarkably great. It is of interest that Wang *et al.*[15], who made biweekly determinations of the plasma lipid fractions in cholesterol-fed rabbits during a 5-month period, observed a steady increase in the lipid concentrations until about the 40th day and then there occurred a leveling-off.

Our observations showed that a relatively early consequence of a high cholesterol fare, besides the increases in plasma and liver cholesterol, was a profound increase in the plasma phospholipid and a significant decrease in liver phospholipid concentration, whereas the aortic phospholipid concentration was unaltered. The derangement in plasma and liver lipid partition obviously reflected disturbances in the "steady state" of the organism and alterations in related metabolic mechanisms. Some evaluations of the nature of the alterations with regard to phospholipid metabolism are possible from the isotopic data of this study. The results showed that the cholesterol-fed, saline-injected rabbits synthesized larger quantities of liver phospholipid, and the plasma phospholipid turnover was greater than in rabbits provided with a control-diet. Since the liver is believed to be the main site for the production as well as the utilization of plasma phospholipid, it may be concluded that the exchange of phospholipid between liver and plasma was accelerated in the cholesterol-fed saline-injected rabbits. It is notable, in this regard, that the liver phospholipid concentration of these animals was significantly less than the controls. One possible explanation of this result is that the increased synthesis of liver phospholipid was accompanied by a much greater increase in phospholipid breakdown. On the other hand, since liver phospholipid is believed to be the immediate precursor of plasma phospholipid, it appears more probable in view of the plasma phospholipid chemical and radioactive data, that the decreased concentration of liver phospholipid found in the rabbits of Group B could be explained by an accelerated exchange between liver and plasma phospholipids with an increase in the absolute turnover of phospholipid (mg. per hour) in the cholesterol-fed rabbits.

The total amount of cortisone administered to some of the rabbits provided the high cholesterol diet was approximately the same as used in similar types of experiments recently reported[10,12,14]. Stumpf and Wilens[14] reported an increase in the plasma neutral fat concentration of cortisone-injected, cholesterol-fed rabbits after approximately 80 days on the high cholesterol diet. They expressed the

*The histological sections of the ascending aorta were examined by Leo D. Moss, M.D., Pathologist, and graded according to severity of degenerative changes observed without foreknowledge of the types of treatment given to the animals.

belief that the high plasma neutral fat might be an important factor in the retardation of arterial lipid deposition observed in these animals. In our results the outstanding difference between cortisone-treated, cholesterol-fed and saline-injected, cholesterol-fed rabbits was the five times greater neutral fat concentration in the plasma and liver of the former group. The mechanisms responsible for these changes cannot be determined from the data of this study; but the altered neutral fat concentrations obviously reflect cortisone's influence on neutral fat transport or mobilization and synthesis, or both. That this condition was extant in the cholesterol-fed rabbits from the inception of the cortisone regimen is apparent from this study and the results of a previous study[6] where an increase of similar extent in plasma and liver neutral fat concentration was found after 2 weeks of cortisone administration to rabbits fed a normal diet *without additives*. In this regard, it is notable that analysis of plasma lipid interrelationships showed that cortisone had not significantly influenced the cholesterol/phospholipid ratio of cholesterol-fed rabbits while the ratio of neutral fat to phospholipid was markedly changed.

The $P^{32}$ data showed that cortisone treatment of cholesterol-fed rabbits induced a 100% increase in the amount of radioactive phosphorus incorporated in the plasma phospholipid compared with cholesterol-fed rabbits without cortisone. However, there was no evidence of an increased turnover of liver phospholipid. The latter would be expected since it is believed that liver phospholipids are the true precursors of plasma phospholipids. On the other hand, the specific activities of liver inorganic and organic acid-soluble phosphate was significantly increased in the cortisone-treated, cholesterol-fed group. The turnover of phospholipid precursors is known to be at least one determinant factor in the availability of $P^{32}$ at the site of phospholipid formation and its incorporation in phospholipid. It appears from these results that the increased turnover of phospholipid precursors in the cortisone-injected, cholesterol-fed rabbits accounted for the increased incorporation of $P^{32}$ in the plasma phospholipids of these animals. It is of interest that these results were different in this respect from our earlier findings[6] in cortisone-injected rabbits furnished a commercial pellet food diet *without additives*. In that study the specific activities of plasma and especially liver phospholipid were markedly elevated. Furthermore, the total liver weight was three times greater in the cortisone-treated rabbits of that study[6] than in controls and the blood glucose level also was significantly elevated. These changes were not found in the cortisone-injected, cholesterol-fed rabbits of this study. Evidently the different dietary regimens had some influence on the nature of the cortisone effects on certain metabolic parameters which were investigated.

With regard to the aorta, except for the elevated total and esterified cholesterol concentrations in the cholesterol-fed, saline-injected rabbits when compared with the respective values of control-diet rabbits there were no differences in either the lipid-metabolic results nor the gross and microscopic anatomical observations. Zilversmit *et al.* recently reported[18] a marked increase in aortic phospholipid synthesis of rabbits after 5 months on a high cholesterol diet. Since our results concerning liver and plasma phospholipid metabolism were essentially in agreement with the findings of Zilversmit *et al.*, an explanation appears indicated for the difference in results with regard

to phospholipid metabolism in the aorta. It is notable, therefore, that the aorta cholesterol content was profoundly increased in the rabbits studied by the latter authors. They reported an average aorta cholesterol of 2.7 gm. per 100 gm. aorta compared with an aortic cholesterol concentration of 0.30 gm. % in our cholesterol-fed rabbits, and a normal aorta cholesterol concentration (in this study and also reported by Zilversmit *et al.*) of 0.16 gm. %. It has been suggested that phospholipids exert a stabilizing effect on the blood lipids, and that plasma phospholipids help to solubilize cholesterol in the plasma[2]. It is possible, therefore, that the significant increase in aortic phospholipid synthesis reported by Zilversmit *et al.*[18] was related to the profoundly increased aortic cholesterol concentration in their rabbits; whereas in our cholesterol-fed rabbits the aortic cholesterol concentration was not remarkably different from controls and the aortic phospholipid synthesis was not modified.

**Summary.** The present study was an attempt to contribute to an explanation of the physiologic mechanisms which may be involved in the pathogenesis of atherosclerosis. The lipid partition and phospholipid turnover in plasma, liver, and aorta were determined in groups of rabbits furnished *for 35 days* a control-type diet, a 1% cholesterol-supplemented diet, and the high cholesterol-diet plus daily intramuscular cortisone administration. The duration of the experimental period was purposefully chosen to correspond with approximately one-half the time usually employed to experimentally induce atheromata in rabbits on a high cholesterol diet. Some lipid-metabolic patterns therefore were investigated at a time before atherosclerosis would be overtly present were the conditions maintained for a longer period.

1) Gross and microscopic atheromata were not found in the cholesterol-fed rabbits without or with cortisone exhibition. 2) A small, but significant increase, in the aortic cholesterol concentration was found in the rabbits fed the cholesterol diet alone compared with those fed the control diet, while the concentrations of the other aortic lipid fractions were unaltered. In the cortisone-injected, cholesterol-fed rabbits the aortic lipid partition picture was the same as those without cortisone treatment. 3) The aortic phospholipid specific activities were similar in the groups on control-diet, high cholesterol-diet alone, and cholesterol-diet plus cortisone. 4) High cholesterol diet alone resulted in elevated concentrations of all plasma lipid fractions except neutral fat, and significantly increased concentrations of liver total lipids and cholesterol fractions; the liver phospholipid concentration, however, was decreased and the neutral fat was not altered; and the plasma and liver phospholipid turnover was markedly greater than in rabbits maintained on the control diet. 5) Cortisone exhibition in cholesterol-fed rabbits induced a marked increase in the neutral fat concentration of plasma and liver while the phospholipid and cholesterol fractions in these tissues were not different from the group on cholesterol-diet alone. 6) The liver phospholipid specific activity in the cortisone-treated group was not different from the group on the high cholesterol-diet without cortisone. The amount of radioactive phospholipid per cubic centimeter of plasma was greater in the cortisone-injected animals than those on the high cholesterol diet alone. This apparently was associated with an increased turnover of liver phospholipid precursors (liver inorganic and organic acid-soluble phosphate). 7) The relative proportion of neutral fat in the plasma lipids of the cortisone-injected, cholesterol-fed an-

mals was markedly elevated as compared to the concentrations of phospholipid and cholesterol, whereas the plasma lipid interrelationships in the rabbits fed the high cholesterol diet alone showed a disproportionate increase in ester cholesterol compared to the alterations in the other lipid fractions. The implications of these findings are discussed in relation to the general problem of the pathogenesis of atherosclerosis.

ACKNOWLEDGMENT is made to Frank Szematowicz, Janice Stoneking, and Muriel Dury for their technical assistance.

REFERENCES

1. **Anitschkow, N.**, and **Chalatow, S.**: Cntralbl. Allg. Path. u. path. Anat., **24**, 1, 1913.
2. **Bruger, M.**, and **Oppenheim, E.**: Bull. New York Acad. Med., **27**, 539, 1951.
3. **Cook, D. L., Mills, L. M.**, and **Green, D. M.**: J. Exper. Med., **99**, 119, 1954.
4. **Cook, D. L., Ray, R., Davisson, E., Feldstein, L. M., Calvin L. D.**, and **Green, D. M.**: Ibid., **96**, 27, 1949.
5. **Duff, G. L.**, and **McMillan, G. C.**: Ibid., **89**, 611, 1949.
6. **Dury, A.**, and **DiLuzio, N. R.**: Am. J. Physiol., in press.
7. **Dury, A.**, and **Moss, L. D.**: J. Gerontol., **9**, 287, 1954.
8. **Dury, A.**, and **Treadwell, C. R.**: Proc. Soc. Exper. Biol. & Med., **82**, 719, 1953.
9. **Fiske, C. H.**, and **SubbaRow, Y.**: J. Biol. Chem., **66**, 375, 1925.
10. **Gordon, D., Kobernick, S. D., McMillan, G. C.**, and **Duff, G. L.**: J. Exper. Med., **99**, 371, 1954.
11. **Nelson, N.**: J. Biol. Chem., **153**, 375, 1944.
12. **Oppenheim, E.**, and **Bruger, M.**: Circulation, **6**, 470, 1952.
13. **Schoenheimer, R.**, and **Sperry, W. M.**: J. Biol. Chem., **106**, 745, 1934.
14. **Stumpf, H. H.**, and **Wilens, S. L.**: Proc. Soc. Exper. Biol. & Med., **86**, 219, 1954.
15. **Wang, C. I., Schaeffer, L. E., Drachman, S. R.**, and **Adlersberg, D.**: J. Mt. Sinai Hosp., New York, **21**, 19, 1954.
16. **Youngsburg, G. E.**, and **Youngsburg, M. V.**: J. Lab. & Clin. Med., **16**, 158, 1930.
17. **Zilversmit, D. B., Entenman, C.**, and **Chaikoff, I. L.**: J. Biol. Chem., **176**, 193, 1948.
18. **Zilversmit, D. B., Shore, M. L.**, and **Ackerman, R. F.**: Circulation, **9**, 581, 1954.

*(Interlingua on page 440)*

## SUMMARIO IN INTERLINGUA

*(See page 392 for original article)*

### Effectos de Kalium e Cortisona Super Morbiditate e Hyponatremia Post Chirurgia Mitrovalvular

1. Es reportate observationes clinic in re le effectos de supplementos de kalium e cortisona super le morbiditate e le responsas metabolic de 12 patientes subjicite a chirurgia del valvula mitral.

2. Le administration de limitate quantitates de kalium, executate in 3 casos, resultava uniformemente in le declaration de leve hyperkalemia.

3. Le administration de cortisona esseva executate in 9 casos. Illo esseva combinate con restringite ingestion de fluido e natrium e non esseva accompaniate de augmento de peso, hyponatremia, o hyperkalemia. In un caso cortisona esseva apparentemente un utile supplemento del intense tractamento de profunde collapso circulatori per medio de aminos pressorial. Cortisona non preveniva pericarditis postoperative.

4. Nos conclude que restringer le ingestion de fluido e de natrium es importante in le tractamento postoperative de patientes subjicite a chirurgia del valvula mitral. Kalium deberea esser limitate al quantitates fornite per le resources natural in tanto que illos es tolerate per le patiente. Cortisona supplementari es possibilemente de valor auxiliar in le casos special de patientes qui se trova sub conditiones de un profunde stress.

# PROGRESS OF MEDICAL SCIENCE

## OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

NOAH D. FABRICANT, M.D.
CLINICAL ASSISTANT PROFESSOR OF OTO-LARYNGOLOGY
UNIVERSITY OF ILLINOIS COLLEGE OF MEDICINE, CHICAGO, ILLINOIS

AND

A. HARRY NEFFSON, M.D.
TUCSON, ARIZONA

## THE PHYSIOLOGICAL APPROACH TO NASAL MEDICATION

BY NOAH D. FABRICANT, M.D.
CLINICAL ASSISTANT PROFESSOR OF OTO-LARYNGOLOGY
UNIVERSITY OF ILLINOIS COLLEGE OF MEDICINE, CHICAGO, ILLINOIS

PHYSICIANS who use and prescribe nasal medication in clinical practice frequently assume that this group of topical medicaments should always react on the mucous membranes of the nasal cavity in a predictable fashion; they are unaware that while nasal medication is pharmacologically constructed to exert a constant and predictable effect, the nasal environment into which nasal medicaments are introduced is far from constant and is continuously subject to change. The degree of response between individual noses given the same dose of a drug may differ, and the response itself may vary from nose to nose and from time to time. Indeed, it is axiomatic that no two noses are alike. From the time the human being is born to the time that he dies, the mucous membrane of his nasal cavity is continuously subjected to the lashings of acute infections, weather conditions, allergens, smoke, dust, and chemical substances. "Normal" respiratory mucous membrane exists only during the first few months of life; it seldom remains normal in the classic sense because of its particular vulnerability to inflammatory and allergic changes[1].

In order to use nasal medication in clinical practice effectively and intelligently, it is necessary to relate these widely prescribed medicaments to various aspects of the nasal environment. Nasal medication should be regarded not only in terms of its inherent pharmacological properties, but also in terms of its local effect on nasal and sinus mucous membranes, ciliary motility, nasal pH, and its systemic effect on the body itself. Although it may be difficult for some physicians to believe in retrospect that they were ever deluded, each medical generation is ac-



UNIVERSITY OF MICHIGAN LIBRARIES

quainted with nasal therapies that have run a generous spectrum of overenthusiasm and disillusionment.

The histopathological changes found in acute inflammation of nasal mucous membranes are similar to those taking place elsewhere in the body. Repeated acute infections eventually lead to chronic infections, and changes in the mucous membranes vary considerably according to the severity and the duration of the infectious process. On the other hand, the histopathologic changes encountered in allergy of the nasal mucous membranes are characterized by edema which involves all the mucosal layers and an eosinophilic infiltration of the tissues, which together with the edema produces alteration in the glands, blood vessels, and the stroma. When a chronic infection is superimposed on an allergic process, changes that represent a combination of allergy and chronic inflammation of the infectious type occur.

Effective nasal medication should not only do what the prescribing physician hopes to accomplish in the patient's nasal cavity without causing injury to the mucous membranes but should also instigate no harm elsewhere in the body. The value of animal experimentation as a basis for observing the histophysiological effect on nasal mucous membranes of various nasal preparations is well recognized but not always practiced. In general, it is highly advisable to determine the physiological and histological effects of nasal medicaments on the normal nasal mucous membranes of experimental animals before advocating their widespread use in human beings. Moreover, since mucous membranes are actively absorbent, it is necessary to guard against systemic reactions from absorption of highly active medicaments. Obviously, drugs that produce toxic reactions after intranasal administration merit small consideration in routine clinical practice. Nasal medicaments that consistently produce unlooked for changes in blood pressure, pulse rate, respiratory frequency, palpitation, general nervousness, tremor and insomnia cannot be considered satisfactory. In this connection, Childrey and Essex[3] have pointed out that absorption from the mucous membranes of the nasal cavity and the paranasal sinuses is much more rapid when these membranes are inflamed. This may offer one possible explanation for an occasional case of sensitivity or idiosyncrasy to nasal medicaments. Fortunately, a great margin of safety accompanies the selection of highly active drugs currently employed in the treatment of various nasal and sinus disorders.

Some years ago Lierle and Moore[8] became interested in determining the effect of drugs commonly used in the nasal cavity on the ciliary action of the nasal mucous membrane. They were among the first of a small group of investigators to study the problem. As a result of their work, they revealed the chaotic state in which nasal therapy then lay slumbering and instituted a reawakening in nasal physiology and rational intranasal therapy. The respiratory mucous membrane of the nasal cavity and paranasal sinuses is ciliated, the ciliated cells traversing the entire thickness of the epithelium and ending superficially in cilia. Biologically, cilia are very ancient structures, vigorous, resistant, and extremely powerful. A thin, overlying blanket of mucus is kept moving in the direction of the nasopharynx by the motion of the cilia. Bacteria and dust deposited on the respiratory mucous membrane are efficiently deposed of by the cilia and the overlying blanket of mucus, which together constitute a veritable belt conveyor. The physical character of mucus, together with its movement,

comprise an extremely effective mechanism against attack by airborne agents, entrapping dust, bacteria, powder, and other inimical agents.

With these facts in mind, the necessity for altering the point of view of treatment of nasal conditions from an exclusively bacteriological to a physiological one becomes apparent. The tendency to assume that nasal medication should always include antibacterial agents under any given circumstances on the theory that the nasal cavity is constantly teeming with pathogenic microörganisms does not square with modern concepts of nasal physiology. For example, Arnold and his associates[1] have observed that when bacteria are sprayed into the nasal cavity, they are swept away very quickly and completely by mucociliary streaming within a few minutes from the active areas. It is for this reason that the deeper portions of the nasal cavity are so often found to be sterile. While the elimination of pathogenic nasal organisms is desirable, and presumably may be accomplished on some occasions by appropriate antibacterial agents, it is necessary to remember in applied clinical practice that the natural defenses of the nasal cavity as expressed by mucociliary action are most helpful.

Tap water and distilled water cause slowing of the ciliary beat when applied to mucous membranes of the upper respiratory tract. A solution of 3% ephedrine hydrochloride is not detrimental to ciliary activity and occasionally increases the ciliary beat. While a solution of 5% cocaine hydrochloride does not interfere with ciliary activity, stronger 10% and 20% solutions prompt definite slowing. Mild silver preparations in concentrations of 5%, 10%, and 20% produce an initial increase in ciliary activity followed by slowing of the beat. Preparations like a 1:1,000 solution of epinephrine hydrochloride and a 2% solution of zinc sulfate are detrimental to the ciliary beat. A 0.25% solution of phenylephrine hydrochloride will not interfere with ciliary activity, nor will ephedrine sulfate in physiological sodium chloride in strengths of 0.5%, 2%, and 3%. There is no appreciable change in ciliary beat when an amphetamine inhaler is used.

According to Proetz[9], ciliary activity continues for long periods of time in 0.9% sodium chloride solution at room temperature. With an increase in concentration of sodium chloride to 4% strength and slightly higher, all activity ceases. However, the ciliary beat can be restored by prompt washing with distilled water followed by normal saline solution. If the concentration of sodium chloride is lowered to 0.2% to 0.3%, ciliary action ceases and the cilia are permanently disabled. Distilled water acts in a manner similar to dilute sodium chloride solutions. Liquid petrolatum (mineral oil) nasal preparations, which for the most part have been discontinued, interfere with ciliary streaming by lying inert on the mucous blanket. Although there is no actual harm to cilia, the inability of mineral oil to mix with mucus burdens the cilia unnecessarily, thereby interfering with its function.

Recognition of Fantus'[6] dictum, that a hydrogen ion concentration near that normal to the mucous membrane is a matter of even greater importance for applications to the mucous membranes than the matter of isotonicity, has provided a firm foundation for sound, physiological nasal medication. The cytological content of nasal and sinal secretions may be considered an approximate index of the pathological processes occurring in the tissues, and the cytological observations provide important diagnostic information. Hansel[7] asserts that in allergy it is especially significant that when the pH falls

low on the acid side, there is a complete disappearance of eosinophils. When pH returns to the alkaline side, there is a return of the eosinophils. Several investigations demonstrate that in allergic patients the pH of nasal secretions changes toward the alkaline side and that nasal secretions from patients with nasal allergy are predominantly alkaline[2]. In general, intranasal treatment by means of sound, physiological medication requires treatment of mucous membrane surfaces (including ciliary action) and treatment of nasal secretions (including mucous blanket). Normal nasal secretions possess a purposeful acid barrier against infection, for it has been shown that acidity as reflected in low pH values is unfavorable to the growth of pathogenic bacteria in the nasal cavity[10].

The manner in which the trend of the nasal pH variation is affected in the nasal cavity by the introduction of a nasal medicament depends entirely on the pH of the drug employed (Fabricant's law). Hence, drugs with a highly alkaline pH induce in the nasal pH variation a pronounced drift toward alkalinity. Drugs with a pH range of 5.5 to 6.5, which approximate the normal range of nasal pH, do not markedly affect nasal pH. Drugs with a pH level of less than 5 induce a drift downward in nasal pH, that is, toward acidity. Fabricant[5] has found that nasal vasoconstrictors possessing an unusually high alkaline pH value may disturb the normal nasal pH level present in clinically normal nasal passages, enhance irritation of the mucous membranes, and postpone the return of the nasal mucous membranes from a pathological alkaline status to a normal, slightly acid status. During an attack of acute rhinitis, acute rhinosinusitis, and the more active stages of allergic rhinitis the use of a nasal vasoconstrictor that lowers the abnormal alkaline nasal pH found in these entities to a normal, slightly acid pH level between 5.5 and 6.5 in adults or 5.0 and 6.7 in infants and children; in short, a true physiological nasal pH; is most desirable for efficacious therapy.

To summarize: the wide acceptance of sound topical therapy of the nasal cavity and its associated paranasal sinuses can only be established in clinical practice by consideration of the physiological approach to nasal medication. Better local therapy rests on knowledge of the effect of nasal preparations on nasal and sinus mucous membranes, ciliary motility, the hydrogen ion concentration of nasal secretions, and by observing the presence or absence of local and systemic side-effects. Nontoxic, nonsensitizing nasal medication that is compatible with ciliary motility, that does not vary greatly in its hydrogen ion concentration from that of normal nasal secretions (pH 5.5 to 6.5), and that is nontraumatizing to the mucous membranes is most desirable in the treatment of the nasal cavity and its diseases. These attributes are most useful in clinical practice precisely because they rely on trustworthy principles underlying sound, physiological nasal medication.

## REFERENCES

(1) **Arnold, L., Ostrom, M. L., and Singer, C. L.:** Proc. Soc. Exper. Biol. & Med., **25**, 624, 1928.
(2) **Buhrmester, C. C.:** Ann. Otol., Rhin & Laryng., **42**, 1041, 1933.
(3) **Childrey, J. H., and Essex, H. E.:** A.M.A. Arch. Otolaryng., **14**, 564, 1931.

(4) **Fabricant, N. D.:** Modern Medication of the Ear, Nose and Throat. New York: Grune & Stratton, 1951. (5) Idem: J. Am. Med. Assn., **151,** 21, 1953. (6) **Fantus, B.:** The Technic of Medication, Chicago: American Medical Association Press, 1938.
(7) **Hansel, F. K.:** Tr. Am. Laryng. Assn., **62,** 292, 1940.
(8) **Lierle, D. M.,** and **Moore, P. M.:** A.M.A. Arch. Otolaryng., **19,** 55, 1934.
(9) **Proetz, A. W.:** J. Laryng. & Otol., **49,** 557, 1934.
(10) **Tweedie, A. R.:** Ibid., **49,** 586, 1934.

## SUMMARIO IN INTERLINGUA

*(See page 427 for original article)*

### Le Effecto de Dieta a Alte Contento de Cholesterol Sin e Con Administration de Cortisona Super le Metabolismo de Phospholipidos e le Partition de Lipidos in Plasma, Hepate, e Aorta de Conilios

Le partition de lipidos in plasma, hepate, e aorta e le metabolismo de phospholipidos esseva determinate in gruppos de conilios que habeva recipite durante 35 dies (a) un dieta de controlo, (b) un dieta supplementate per 1 pro cento de cholesterol, o (c) iste mesme dieta con diurne administrationes intramuscular de cortisona. Le studio esseva interprendite como contribution al explication del mechanismo physiologic de atherosclerosis.

1. Atheromas aortic non esseva observate in le conilios de ulle gruppo.

2. Le sequente alterationes in comparation con le conilios de controlo esseva incontrate in le gruppo a dieta cholesterolic sin cortisona: Un parve sed significative augmento de solmente le aortic concentration de cholesterol habeva occurrite. Omne fractiones lipide del plasma e del hepate, con le exception de grassia neutre, esseva alterate de maniera significative. Determinationes per medio del traciator radioactive $P^{32}$ monstrava que le metabolismo del phospholipidos aortic non esseva alterate durante que le mesme metabolismo in plasma e hepate esseva marcatemente elevate.

3. In le conilios mantenite super un dieta a cholesterol combinate con administrationes de cortisona nulle alterate partition del lipidos aortic esseva observate in comparation con le conilios recipiente le mesme dieta sed nulle cortisona. In le conilios del prime de iste gruppos le concentration de grassia neutre in plasma e hepate esseva significativemente augmentate, sed nulle tal differentia esseva trovate in le caso del altere fractiones lipide. Le quantitate de $P^{32}$ incorporate in le phospholipidos del plasma esseva significativemente elevate in le conilios tractate con cortisona. Iste facto esseva associate con un augmentate metabolismo del precursores de phospholipidos hepatic.

4. Nos discute le implicationes de iste constatationes in relation al problema general del pathogenese de atherosclerosis.

## DERMATOLOGY AND SYPHILOLOGY

UNDER THE CHARGE OF

JOHN H. STOKES, M.D.
EMERITUS PROFESSOR OF DERMATOLOGY, GRADUATE SCHOOL OF MEDICINE
UNIVERSITY OF PENNSYLVANIA

HERMAN BEERMAN, M.D.
PROFESSOR OF DERMATOLOGY, GRADUATE SCHOOL OF MEDICINE
UNIVERSITY OF PENNSYLVANIA

AND

NORMAN R. INGRAHAM, JR., M.D.
ASSOCIATE PROFESSOR OF DERMATOLOGY, GRADUATE SCHOOL OF MEDICINE
UNIVERSITY OF PENNSYLVANIA
PHILADELPHIA, PENNSYLVANIA

# SOME ASPECTS OF DERMATOLOGY IN NEUROLOGY

BY HERMAN BEERMAN, M.D.

(From the University of Pennsylvania, Departments of Dermatology, School of Medicine; Donald M. Pillsbury, M.D., Professor, and Graduate School of Medicine; Herman Beerman, M.D., Chairman, Philadelphia, Pennsylvania)

NEUROLOGISTS are better acquainted with the often bizarre neurologic symptoms and signs that occur in conjunction with a variety of changes in the skin. In many instances, however, recognition of the cutaneous disorders may lead to the analysis of the basic underlying fault. Thus the presence of vasomotor phenomena, pigmentary changes, scars, hypertrichosis and alopecia may contribute much toward the neurologic diagnosis. This association of cutaneous and nervous system abnormalities is not surprising when one recalls that the skin and nervous system have a common embryonic origin: the ectoderm. Accordingly, developmental errors may result in abnormalities in one or both of these ectodermal derivates.

In addition to this common origin, the nervous system plays an important role in the initiation and control of certain cutaneous functions, sensation, secretion, temperature regulation, and others. Under abnormal circumstances, the nervous system may influence the course of a purely cutaneous disease. In this presentation we will discuss the role of the nervous system in normal cutaneous function and disease (psychosomatic), diseases of nerve structures in the skin, diseases of the skin with neurological manifestations, and diseases of the nervous system and skin (neurocutaneous syndromes). In passing it is worth noting that the skin is a tool of value in neurologic diagnosis. Although the eye is essentially an appendage of the nervous system which affords interesting correlations with the skin, the diseases of the eye and skin *per se* will not be included in this survey. Furthermore, many aspects of the subjects under consideration will not be detailed.

It is obvious that in many instances the occurrence of nervous system and

cutaneous disorders simultaneously may be mere coincidence. While in many such cases the incidental character of the relationship will be pointed out, it is also clear that in a number of instances what appears to be coincidence is in reality of too frequent occurrence to be dismissed as being without causal relationship.

The multiplicity of the processes with both cutaneous and neurologic counterparts can be judged by scanning even a partial list of dermatologic eponyms. For example, in Haberlin and Garrard's[59] recent compilation, the following are among those falling into this category: Balzer's adenoma sebaceum; Bloch-Sulzberger disease (incontinentia pigmenti); Bushfield-Wyatt syndrome (Sturge-Weber syndrome); Cushing's disease; Dercum's disease; Erb's syndrome; Frey's syndrome; Grönbald-Strandberg syndrome; Hand-Schüller-Christian disease; Hansen's disease; Hunt's syndrome; Hutchinson's syndrome (triad); Letterer-Siwe disease; Morvan's disease; Parkes-Weber syndrome; Quincke's disease; Romberg's disease; Vogt-Koyanagi syndrome; von Recklinghausen's disease and Waterhouse-Friederichsen syndrome. In addition to this partial list of "named" diseases and syndromes, there are numerous other nervous and cutaneous disorders but only a selected few of them will be discussed in some detail.

SKIN AS AN ORGAN OF SENSE. The skin participates in four chief modalities of sensation: pain (prickling, burning pain, itching and possibly tickling), touch, cold and warmth. The fundamental interrelationships of these modalities and their pathways are still uncertain but for purposes of this discussion, it suffices merely to indicate how profoundly the nervous system is involved in these phenomena and their mechanisms so that derangements in any of them may be the indication of underlying nervous system disease both central and peripheral.

CIRCULATION. The influence of nervous elements (sympathetic) in vasoconstriction and those (parasympathetic, dorsal root, and sympathetic vasodilator fibers) causing vasodilatation is well recognized. The details need not be given here. Variations in the functions of these pathways play important roles in certain neurocutaneous disorders[120,121].

As will be mentioned later, vasoconstriction is, to a large extent, a function of the sympathetic nervous system but pain, emotional stress, surgical shock, malnutrition, and exposure to cold increase vasomotor tone. Vasoconstriction influences are additive and the presence of a high tone intensifies the action of a vasoconstrictor agent. Because of the great clinical importance of digital ischemia, a prime correlate of skin and nervous system, the table of causes of digital ischemia compiled by Edwards[40] is reproduced (Table 1). Although there is still controversy regarding the pathology and pathogenesis of these diseases, the table represents a working guide based on present knowledge. For details, the reader is referred to Edwards' excellent paper.

ABSORPTION. Aside from the combined diseases of the skin and nervous system, the skin may absorb certain substances which in turn may produce nervous symptoms, or certain drugs when given by mouth or otherwise may cause cutaneous and nervous system symptoms (for example ACTH and cortisone). The local application of asterol dihydrochloride ointment to the skin, usually in infants, has caused toxic encephalopathy[137], muscular spasms especially of the extremities, visual hallucinosis, depression of sensorium functions[63] and convulsions[47].

SWEATING. Most everyday sweating

TABLE 1.—CAUSES OF DIGITAL ISCHEMIA

| *Primarily Obstructive Causes* | | | *Primarily Functional Causes* | | | | | |
|---|---|---|---|---|---|---|---|---|
| *Major Arteries* | *Fine Vessels* | *Blood Agglutination* | *Cold Sensitivity and Cold Exposure* | *Nervous System* | *Reflex Constriction* | *Metabolic and Adynamic* | *Hormonal* | *Pharmacologic* |
| Arteriosclerosis | Scleroderma | Dyscrasias (polycythemia, leukemia, thrombotic thrombocytopenic purpura) | Raynaud's disease | Stress & mental disease (livedo reticularis, hyperhidrosis, acrocyanosis) | Spinal arthritis | Rheumatoid arthritis | Hypothyroidism | Tobacco smoking |
| Embolism (from heart or aneurysm) | Polyarteritis | Cold reactions (frostbite, cold agglutinins, cryoglobulinemia) | Cold urticaria | Poliomyelitis | Causalgia and minor causalgia | Malnutrition & asthenia | Castration | Ergotism |
| Thromboangiitis obliterans | Disseminated lupus | Idiopathic (necrotizing acrocyanosis) | Trench and immersion foot | Hemiplegia | Shoulder-hand syndrome | Terminal rheumatic heart disease | Menopause | |
| Injury (Volkmann's contracture) | Dermatomyositis | Massive venous thrombosis | | Tumor | "Vibrating-machine disease" | | Addison's disease | |
| Neurovascular compression at root of upper limb (cervical rib & scalenus, costoclavicular & hyperabduction syndromes) | Chilblains | | | Multiple sclerosis | | | | |
| | Syphilis | | | (?) Epileptic equivalent | | | | |
| | Radiation injury | | | Peripheral neuritis | | | | |
| | | | | Post-trench-foot and post-frostbite syndromes | | | | |
| | | | | Spina bifida | | | | |

is practically all the result of nervous impulses. A certain amount, however, is non-nervous, due to local glandular response. Sweating due to nervous excitation is a reflex phenomenon mediated through an axon reflex, intrasympathetic reflex, spinal or bulbar reflex, and diencephalic or cortical reflex. Direct stimulation of sweat glands results in sweating restricted to the area stimulated. Nervous sweating, on the other hand, is more widespread. In axon reflex sweating, the size of the responding area depends on the sum of the hands, and chest and neck, and is least in the palms and the soles. On the other hand, emotional or sensory stimuli produce sweating which is largely confined to the palms and soles, though it may also occur in the axillae. Both types of sweating are under the control of the central nervous system, thermal sweating by the temperature regulating center in the anterior portion of the hypothalamus and mental sweating by centers not yet accurately localized but possibly situated in the cerebral cortex. These centers

TABLE 2.—ETIOLOGIC CLASSIFICATION OF ANHIDROSIS

| *Site of Disturbance* | *Pathologic Change* | *Examples* |
|---|---|---|
| Brain | | Heat stroke |
| Cerebrum | | Hysteria |
| Hypothalamus | | Organic lesion (neoplastic, vascular) |
| Medulla | | |
| Pons | | |
| Spinal Cord | Interruption of Pathways | Multiple sclerosis |
| Lateral reticulo-spinal tract | | Myelitis |
| Intermedio-lateral horn-cells | | Organic lesion |
| | | Poliomyelitis |
| | | Syringomyelia |
| | | Transection |
| Peripheral Nerves | Interruption of Pathways | Alcoholic polyneuritis |
| Pre-ganglionic fibers | | Anticholinergic agents (atropine) |
| Post-ganglionic fibers | | Leprosy |
| Adenoneural junction | | Organic lesion |
| | | Sympathectomy |
| | | Tetra-ethyl ammonium |

number and unification of the axon reflexes which have been stimulated. The area supplied by the excited ganglia will respond in the case of intrasympathetic reflex sweating. Spinal reflex sweating appears as a segmentary arrangement. In the diencephalic reflex type of sweating the distribution is general. The details of this important subject are covered by Rothman[105b].

Kuno[75] has shown that there are two fundamentally different types of stimuli which evoke two quite different types of sweat response. Heating the body leads to profuse sweating, which is most marked on the forehead, dorsum of the hands, and chest and neck, and is least in the palms and the soles. On the other hand, emotional or sensory stimuli produce sweating which is largely confined to the palms and soles, though it may also occur in the axillae. Both types of sweating are under the control of the central nervous system, thermal sweating by the temperature regulating center in the anterior portion of the hypothalamus and mental sweating by centers not yet accurately localized but possibly situated in the cerebral cortex. These centers act via descending pathways within the central nervous system which finally relay around connector cells belonging anatomically to the sympathetic system, and therefore situated in the lateral horn of grey matter between the first thoracic and second lumbar segment, respectively, of the spinal cord. After transection of the spinal cord these cells may function independently to produce the profuse sweating characteristic of the "mass reflex" response.

The innervation of the sweat glands forms part of the sympathetic nervous system but it has been long known

that the responses of these glands to drugs closely resembles those of glands under the control of the parasympathetic nervous system. Chalmers and Keele[27] found that the innervation of sweat glands in man appears to be entirely cholinergic.

ANHIDROSIS. In addition to the changes in the nervous control of sweating resulting in hyperhidrosis, recent attention has been directed to anhidrosis[113] or "the inability of the body to produce and/or deliver sweat to the skin surface. It is characterized clinically by the absence of visible sweat on the skin in the presence of an appropriate stimulus and environment."

Shelley and his co-workers have described the occurrence of anhidrosis due to changes in the nervous system (see Table 2). Although but little is known with certainty, it would appear that the frontal lobes have an influence on sweating, often inhibitory in nature. The cerebral cortex also plays a role (cortex of the post-central gyrus has a contralateral inhibitory effect on sweat function)[92]. Hysterical and physical anhidrosis has been reported. The hypothalmus as a heat regulating center may be responsible for anhidrosis because of tumors or injury (operations or otherwise), or heat stroke (sweat retention syndrome). Lesions of the lateral medulla or pons lead to anhidrosis of the face and neck of the same side and of the body on the same or opposite side. Organic lesions affecting the involved tract by fibers or nerve cells in the spinal cord may manifest areas of anhidrosis due to an interruption of the reflex arc. Because of overlap of innervation, the lesions must be extensive before clinical effects can be seen. Poliomyelitis, multiple sclerosis, syringomyelia, myelitis and spinal cord tumors are examples of processes in which anhidrosis may occur as a result of damage to the nervous pathways. Transection of the cord is followed by complete but temporary anhidrosis.

From the previously described autonomic nervous system influence on sweating, it would not be surprising that interruption of such fibers (surgical or traumatic) would lead to anhidrosis. Because of extensive overlapping of adjacent roots there may be no demonstrable effect. However, disease, alcoholic polyneuritis, tumors or injury of the sympathetic nerve fibers may occur with anhidrosis. In this connection, for example, Arnold[3] has found that the intradermal injection of metacholine chloride solution and evaluation of the resulting sweat response constitutes a useful method of demonstrating the presence and extent of peripheral sympathetic nerve damage. Normal response is rarely met with even in very early lesions of tuberculoid or indeterminate macular leprosy. Abnormal response probably precedes the onset of demonstrable sensory changes. This is a substitute for the histamine test. Nerve block, Horner's syndrome (disruption of the cervical ganglia), chemical sympathectomy (hyoscine and homatropine), and tetraethyl ammonium chloride or bromide may produce anhidrosis.

SEBACEOUS GLAND SECRETION. Human sebaceous glands are supplied with nerves going both to the surrounding connective tissue and to the gland itself, some of them actually forming a plexus on the basement membrane of the gland. In spite of the anatomical make-up, there is no direct evidence for secretory innervation of sebaceous glands. The belief, long held, that postencephalitic seborrhea was due to destruction of an inhibitory center for sebaceous glands in the diencephalon, has been laid to rest by the work of Miescher and Schönberg[88]. Further

clinical evidence of the nervous control of sebum secretion is inconclusive, for example, increased sebum flow in the area supplied by the supraorbital nerve occurring after an injury with complete severance of the nerve; or unilateral occurrence of acne vulgaris and seborrhea subsequent to facial palsy on the affected side. Lately the claim that emotions increase sebaceous secretion has been subjected to critical evaluation and as yet does not rest on a firmly established basis since the results are intermixed with emotional hyperhidrosis.

PIGMENTATION. The nervous system also plays an increasingly important role in pigmentation. This is more apparent in abnormal states than in the case with normal skin. For example, one need only recall the linear nevi with pigmentation following certain cutaneous nerves[67b], and Haxthausen's[61] concept of a neurotrophic basis for vitiligo. This neural influence on pigmentation is probably due to the close association embryologically between nervous tissue and melanin-forming cells. The proof of neural control over melanogenesis is, however, inconclusive. The more recent demonstration of the importance in the pigment problem of the pituitary glands is to the point. It is not known for certain whether this gland exerts its effect by acting on other endocrine glands or through the melanocyte-stimulating hormone (MSH, melanophore hormone, intermedin), which has recently been proved to have an actual effect in stimulation of pigmentation in animals[49,78,114].

*Kernicterus.* Kernicterus[13,46,54,141,145] associated with jaundice from whatever cause is characterized by a normal child at birth, jaundice before the second day, central nervous system involvement with convulsions, spasticity and apnea, and death before the sixth day. Kernicterus may be associated with erythroblastosis. The neurological signs and symptoms are due to involvement of the basal ganglia third nerve nuclei, and parts of the medulla and cerebellum, and even parts of the spinal cord.

Skin discoloration may be of great value in neurologic diagnosis. Leavitt[76] classified the significance of skin discoloration as follows: (1) direct relationship between discoloration and neurologic disease, for example, herpes zoster; (2) discoloration as a facet of a hereditary or congenital neuropathologic process, such as "cafe au lait" spots in von Recklinghausen's disease, and nevi associated with hemangiomas; (3) discoloration as an intrinsic component in a neurologic syndrome, for example, vasomotor changes of the skin in autonomic nervous system disorders; (4) discoloration as a primary manifestation in diseases which secondarily involve the central nervous system, for example, hemorrhagic disease; (5) discoloration as a secondary manifestation in diseases which primarily involve the central nervous system, for example, "rose spots" of cerebrospinal meningitis. A full discussion of the differential diagnosis of cutaneous hyperpigmentation would include all with neurological counterparts or associates such as vitamin deficiencies (pellagra), acanthosis nigricans, scleroderma, anemias, certain lipidoses, pituitary syndromes and neurofibromatosis. Most of these will be or have been mentioned elsewhere in this review.

HAIR. There is no evidence for the existence of special nerve fibers, necessary for the health and development of hair follicles. Changes in the hair, density or length, after diseases of the nervous system are probably due to vascular disturbances[50,104].

THE AUTONOMIC NERVOUS SYSTEM IN

CUTANEOUS DISEASE. A good example of how profoundly the skin in health and disease is affected by the nervous system is especially apparent in the case of the autonomic nervous system. Rothman[105a] has analyzed this relationship in detail. Fear, anger and rage cause constriction of the pilomotor muscles. This effect of emotion, more apparent in dogs and cats than in men, has a subcortical center in the hypothalmus. The impulse descends through the brain stem and medulla, and leaves the spinal cord in the anterior or roots. It reaches the periphery via sympathetic pathways. This pilomotor reaction is usually associated with vasoconstricting impulse causing paling of the skin in spots around the erected follicles and hairs. A third type of autonomic impulse to the skin is carried by the secretory fibers of the sweat glands. The fourth type of autonomic impulse which produces vasodilation in the cutaneous arterioles is the most important. The fifth type is still less understood. Excessive seborrhea associated with infectious encephalitis and post-encephalitic Parkinsonism is accompanied by destructive lesions in the midbrain and pons. It is probable that the distinctive lesion acts by abolishing a center of inhibition for sebaceous secretion.

These various autonomic pathways have much to do with peripheral phenomena such as pilomotion, hyperhidrosis (emotional), exaggerated blushing (emotional urticaria), and temporary vasoconstriction. This temporary vasoconstriction as well as vasodilatation may be prolonged by external stimuli, particularly vasoconstriction by cold and vasodilatation by warmth. Thus a process ("dead finger") initiated by an emotional response may act in combination with cold. Therefore, it is important to differentiate functional vasoneurosis from Raynaud's disease. In erythromelalgia, attacks of painful redness may be elicited by emotional dilator impulses but this process will not arise without the presence of an organic nerve injury. Emotional vasomotor and other autonomic impulses in themselves are incapable of producing necrotic processes and permanent inflammatory bullous or vesicular reactions. However, though the autonomic impulses are short lasting, they may interfere with the course of a disease which is present independently from emotions, such as an infectious disease or a disease of metabolic or allergic origin. Williams[136] has propounded a concept of allergy as autonomic dysfunction. The effect of emotion on virus disease, for example, herpes simplex, verrucae, and others, is not at all understood.

LESIONS OF NERVES IN THE SKIN. The cutaneous nerves and end organs are all susceptible to pathologic change yielding what would be construed as a disease in the purview of dermatology. Stump neuroma, glomus tumors (angiomyoneuroma), ordinary neuromas of the skin, von Recklinghausen's disease (see below), cellular nevus, neuronevus, neuronevus bleu, and ganglioneuroma of the skin have all received considerable attention. The last mentioned process is the only one of these which we will discuss later. In addition, attention should be called briefly to neurilemmoma and tumors of tactile end organs (including Pacinian neurofibroma).

Montgomery and O'Leary[90] employed the designation, "multiple ganglioneuromas of the skin," to describe a case characterized by multiple cutaneous tumors, composed of a mixture of inflammatory cells and many large pale-staining cells with vesicular nuclei. Granules were demonstrated in the cytoplasm of these cells. These were interpreted as being Nissl's granules and the cells were thought to be

of neural origin, probably ganglionic. Since this case was reported, others have written up similar examples which were identical clinically but which, from the facts, were considered to be reticulohistiocytomas[26,56,142].

Neurilemmoma was generally considered to be a rare tumor of the nerve sheath. Pathologists, on the alert for this process, have been encountering an increasing number of such cases. They have been called by a variety of names, including neurinoma, peripheral glioma, schwannoglioma and schwannoma. Stout and his colleagues[17,122] have reported on the nature of this process as well as on a case involving the nasal septum.

Another rare tumor is that which consists of tactile end organs. Cammermeyer[24] described a tumor removed from the finger of a 50-year-old man. This lesion consisted of conglomerates of highly differentiated tactile end organs with silver-impregnable nerve fibers, which were encapsulated in great masses of connective tissue. Prichard and Custer[101] described two apparently benign tumors of the skin in which structures resembling Pacinian corpuscles were conspicuous. They likewise presented pigmented features common to ordinary pigmented nevi.

DISEASES OF THE SKIN WITH NEUROLOGICAL MANIFESTATIONS. There are numerous processes involving the skin with which manifestations of nervous system disease are frequently associated. Undoubtedly many times this association may be coincidental but in a large number of cases the association is too constant to be considered as due to chance Although there are processes in which neural involvement is a regular feature, in a certain percentage of cases, for example, syphilis, no particular discussion of these diseases is needed except to note that even now unusual examples of one or another manifestation of central nervous system involvement is reported[91] (for example, an unusual case of syphilitic Parkinsonism). The same applies to leprosy, in which disease many new manifestations or description of newer lesions can be found in the recent literature[96].

*Metabolic Diseases.* With respect to metabolic diseases, the dyslipidoses may on occasion be associated with epilepsy (xanthoma tuberosum)[131b] or pituitary involvement[8b], Hand-Schüller-Christian disease, diabetes insipidus, or other nervous system lesions (Niemann-Pick's disease).

Gargoylism, also known as Hurler's syndrome, lipochondrodystrophy or dysostosis multiplex is defined by Washington[134] as a disease of congenital origin characterized by chondrodystrophic changes in the skeleton with a tendency toward the deposition of a lipid substance in the tissue, particularly in the brain. The finding of almost identical nerve cell changes in a variety of conditions (Gaucher's disease, Niemann-Pick's disease, amaurotic idiocy and gargoylism) raises the question of the extent to which the central nervous system changes are specific. However, the majority of the reported patients are mentally defective to a variable degree. Many have normal intelligence and an occasional patient exhibits intelligence greater than normal. About one-quarter of the reported patients show no central nervous system and ocular involvement. Cole and his co-workers[30] who have reported two cases of gargoylism with cutaneous changes, furrowing of skin over lateral thorax in one and the coarse hair and skin on the face in the other, contend that this condition is basically a disease of collagen connective tissue rather than a form of lipochondrodystrophy.

Pellagrins in relapse often manifest psychotic changes. Frostig and Spies[51],

for example, have described the association of so-called psychoneurotic symptoms with subclinical and mild pellagra. Many patients with such symptoms are diagnosed as "neurasthenics." These authors classified their cases as follows:

(*a*) THE ELEMENTARY SYNDROME
1. Psychosensory disturbance
2. Psychomotor disturbance
3. Emotional disturbance

(*b*) GENERAL SYMPTOMS OF THE CENTRAL NERVOUS SYSTEM
1. Weakness and increased fatigability
2. Sleeplessness
3. Headaches

Sjögren's syndrome[10] is a rare systemic disorder combining a group of functional disturbances affecting embryonic derivates of ectodermal and entodermal tissue. It is related to vitamin A and B deficiency as well as disturbances in mineral metabolism and endocrine dysfunction. In 1933, Sjögren[117] first described this process as a chronic disorder characterized by lessened or absent secretions of salivary and lachrymal glands, with dryness of eyes, oral mucous membrane and upper respiratory tract. Behrman[10] described the first American case. According to the Dalsgaard-Nielsens[35] as well as Bruce[21], Sjögren's syndrome represents a disturbance of the sympathetic nervous system.

*Lupus Erythematosus.* Involvement of the central nervous system in cases of systemic lupus erythematosus is not well understood although it is not a rare complication. Sedgwick and Von Hagen[110], in 1948, reviewed the neurology of lupus erythematosus. Glaser[55] recently reviewed the literature and noted that the following neurological findings had been reported: Widespread seizures, convulsive attacks, transient cranial nerve paralysis, hemiparesis and aphasia, acute toxic psychosis, delirium, and cerebrovascular accidents. The pathologic basis for these manifestations of central nervous system involvement, according to Glaser, is "a focal or disseminated encephalomalacia primarily involving the grey matter of the cerebral cortex and secondary to the specific endarteritis." The effect of cortisone and ACTH in the production of these symptoms by acting on a vascular lesion is not yet determined. Russell, Haserick and Zucker[108] had previously noted grand mal epileptic attacks in 6 of 23 lupus patients with positive L.E. test reactions. On the basis of this observation they contend that any patient with epilepsy and rheumatoid arthritis may have systemic lupus erythematosus. In their review of the literature since 1935, among the 144 patients represented, 22 (15%) were reported to have convulsions. Fifteen patients had isolated grand mal seizures during the active, preterminal phase. In their own series since February, 1949, 28 patients with positive reactions in plasma L.E. tests had been observed in the Cleveland Clinic. Seven of these patients had convulsions. Electroencephalograms frequently demonstrated an organic type of dysrhythmia in patients with or without convulsions in systemic L.E. Positive pathologic slides have failed to reveal specific brain alterations in L.E. The authors found that cortisone and ACTH produced improvement in epileptiform seizures related to lupus erythematosus. Lewis, Sinton and Knott[79], found abnormalities in 42 of 51 patients with disorders of collagen (including lupus erythematosus and dermatomyositis). Likewise Tumulty[129] found that of 105 patients with systemic lupus erythematosus studied at Johns Hopkins Hospital, 20 had psychotic episodes of a major sort, 18 had convulsive seizures,

and in 3 hemiplegia developed. Transient cranial nerve palsies also occurred. Peripheral neuritis was uncommon, as were cord lesions. Tumulty points out wisely that not all neurologic findings in patients with lupus erythematosus need be manifestations of that disease. "Every such manifestation of central nervous system disorder must be investigated on its own merits as to cause." Jessar, Lamont-Havers and Kagan[68] also found neurologic or psychiatric manifestations in 18% of 44 patients with lupus erythematosus disseminatus from the Columbia Presbyterian Medical Center of New York.

Pier[99] described a 19-year-old patient with disseminated lupus erythematosus who developed vascular involvement of the spinal cord with infarction and consequent paralysis of the legs.

*Scleroderma.* Although in the past a number of nervous system manifestations (central and peripheral) of scleroderma have been reported, these are certainly uncommon. Furthermore, their exact relationship to scleroderma is much less well established than the associated lesions in some other organs. The same considerations apply to the later literature. In Kanee's case[69], Duryee, in personal communication, reported that electroencephalographic studies revealed a moderate degree of diffuse electrocortical activity. Duryee has found this in over 80% of cases of generalized scleroderma. Duryee and Leinwant (cited by Taylor and Pacella[127]) found the incidence of electroencephalographic abnormalities far higher than in the normal adult population. Taylor and Pacella[127] likewise found among their 56 patients with scleroderma that the proportion of abnormal electroencephalograms (84%) is far higher than might be expected in a series of clinically normal individuals who show only about 10 to 15%. In a later study, Leinwant, Duryee and Richter[77] pointed out that "to date we have no positive autopsy findings to correlate with electroencephalographic findings." Bevans stated that "changes in the central nervous system were studied extensively by Dr. Abner Wolf and were not considered noteworthy in the present connection. Unfortunately, the sympathetic ganglia were not studied. The sympathetic plexuses in the gastrointestinal tract showed no structural alteration. Whether lesions of the sympathetic system are responsible for the spasm exhibited roentgenologically in the gastrointestinal tract awaits investigation. To date the results of sympathectomy for Raynaud's syndrome in patients who develop scleroderma have been variable and not encouraging." Guss[57] reported, in 1947, what he considered to be the second patient with scleroderma in whom convulsions occurred. From the facts and the author's own analysis, this patient's disorders really had a vascular rather than neurogenic origin. At any rate the precise sclerodermatous nature of the nervous system manifestations in this case is not evident. Rubin[107] reported 13 cases of linear scleroderma with abnormalities of the spine and nervous system. In the majority of the cases the lesions lay in the long axis of spinal root zones and less frequently followed the distribution of peripheral nerves.

*Miscellaneous Cutaneous Diseases.* There is a group of rare cutaneous diseases in which neurological changes have been observed often enough to deserve discussion. They are pseudoxanthoma elasticum and incontinentia pigmenti. Although the Vogt-Koyanagi syndrome which ordinarily consists of uveitis, alopecia, vitiligo, poliosis and dysacousia, is thought to be due to a neuropathic factor, no further discussion of it will be made[82]. The same ap-

plies to Melkerssen's syndrome: facial paralysis, edema of the upper lip and lingua plicata[119], to pituitary basophilism in the juvenile type of acanthosis nigricans[105c], and epithelioma adenoides cysticum, basal cell nevi, dental cysts and agenesis of the corpus callosum[12].

*Pseudoxanthoma Elasticum.* This disease is well known to dermatologists and ophthalmologists. Szymanski and Caro[126] summarized the neurologic findings in the literature as well as their case. The brain itself is never involved in pseudoxanthoma elasticum, but symptoms referable to the central nervous system may develop from changes in the cerebral blood vessels. Psychoses and strokes with hemiplegia and hemiparesis have been reported but there is no evidence to substantiate the claims that elastic tissue degeneration is completely responsible. Urbach and Wolfram[132] report the case of a 44-year-old man with pseudoxanthoma elasticum and streaks who suffered with parasthesia in the right arm, recurring spells of blindness and vomiting combined with headaches. Four days before his death of a cerebral accident, he was hospitalized with a Korsakoff-like psychosis. At necropsy, the vessels of the brain showed arteriosclerosis with only slight elastic tissue alteration. It is probable that the arteriosclerosis was responsible for the cerebral manifestation. Holm[64] reported a 39-year-old man with typical skin and eye changes. He had a history of severe hematuria. He died shortly of apoplexy and left-sided paresis due to cerebral hemorrhage. No postmortem examination was made. Dixon's[37] patient was a 29-year-old Negress with pseudoxanthoma elasticum and angioid streaks. She complained of right-sided headache and ptosis of the right eyelid that had appeared suddenly a few days previously. Sixteen days after the onset she developed total paralysis of the right oculomotor and abducens nerves. An angiogram revealed an aneurysm at the upper end of the right internal carotid artery at the point of its entrance into the cranial cavity. This was relieved by surgery. Szymanski and Caro's patient, a 75-year-old obese Cuban woman, had hypertension and developed a stroke. Hypertension is not uncommon in these patients.

*Incontinentia Pigmenti.* Incontinentia pigmenti is a rather rare cutaneous disorder, probably developmental in origin and characterized by a "striking and bizarre arrangement of pigmented macules in polyangular flecks, whorls, spidery forms, lines and patches. These chocolate brown designs do not follow lines of cleavage or distributions of nerves, nor do they respect the limitations of the mid-line. Areas of alopecia in the scalp appear frequently and many other ectodermal and mesodermal defects occur, although they are less well known." Since Bardach in 1925[7], Siemons[115] as well as Bloch in 1926[14], and Sulzberger in 1928[123] presented the earliest known cases of this process, neurologic manifestations have been permanently associated with it. Carney[25], in his excellent study of the literature and his own cases, found the following developmental defects in the 37 cases included in his report: Delayed or imperfect dentition, 11 cases; osseous deformities, 8; alopecia, 7; spastic paralysis, 7; strabismus, 5; epilepsy, 4; microcephaly, 4; mental deficiency, 4; retarded growth and development, 3; corneal opacity, 3; dystrophia unguim, 3; cataracts, 2; optic atrophy, 2; blue scleras, 2; nystagmus, 2; follicular atrophoderma, 2; and single instances right sided headache and ptosis of the of retrobulbar glioma, congenital heart disease, urachal cyst, absence of retinal pigment, supernumerary ears, and nevoid patch of the retina. In 5 of the cases there were no developmental de-

fects and in 10 other cases the reports are equivocal or incomplete. Likewise, Loveman, Fliegelman, Weidman and Rein[83] found various anomalies in their patients with the disease, as well as in other members of the same family. Convulsions and hemiplegia, and other neurologic phenomena were observed in subsequent reports[6,38,44,58,73,98]. It would thus appear that incontinentia pigmenti is one of the cutaneous manifestations of a congenital disorder which affects various structures of ectodermal and possibly mesodermal origin. Ito[67a,b] postulates that it is a congenital dysfunction of the autonomic nervous system and is of the opinion that any inflammatory eruptions of incontinentia pigmenti may occur as the result of the reaction of this congenitally abnormal autonomic nervous system to various stimuli given in the extrauterine environment.

*Alopecia Areata.* Alopecia areata associated with neurodermatitis is rather rare in spite of the fact that alopecia areata is frequently attributed to nervous dysfunction. Robinson and Tasker[103] report two such cases and feel that further observations of patients with alopecia areata may reveal a more frequent association of this disease with neurodermatitis and other dermatoses in the neurodermatoses group.

*Mongolism.* Dermatologic manifestations of mongolism were studied by Zeligman and Scalia[143]. Based on an experience with 106 Mongoloids, they found as frequent cutaneous manifestation: protruding or fissured lower lip, or both, scrotal or enlarged tongue, acrocyanosis, increased number of creases on palms and soles, xerosis or ichthyosis, keratosis palmaris et plantaris and actinic sequelae. Other skin disorders appeared not to exceed the expected norm, and there was no evidence of a marked tendency on the part of Mongoloids to develop eczematous eruptions.

*Gynecomastia.* Gynecomastia may occur in connection with transverse myelitis[135].

*Congenital Ectodermal Dysplasia.* Although the anomalies observed in *hereditary anhidrotic ectodermal dysplasia* are of ectodermal origin, only rarely have definite defects of the nervous system been found in typical examples of this syndrome. It is true, according to Upshaw and Montgomery[130], that numerous anhidrotic patients have been mentally inferior, but it is commonly believed that the same genetic mutation is not responsible for both of these anomalies.

*Pemphigus.* Baló and Földvàri[5] studied 15 cases of pemphigus at necropsy, and found ganglionic cysts of millet grain to pea size, mostly in the median part of the ganglion, near the posterior root. Cysts were seen mostly on dissection of the ganglion but sometimes the ganglions were enlarged enough to be visible to the naked eye. The walls were mostly fibrous tissue. Some cysts were lined by a layer of myelinic fibers. The ganglion cells were also affected. Proliferation of satellite cells were seen. In some cases, the capsule around the ganglion cells was thickened due to proliferation of connective tissue. In addition, other changes were evident. Sulzberger and Baer[124] do not feel the facts of pemphigus fit in with the neurogenic theory.

INFECTIONS. As mentioned previously, infections often present nervous system manifestations. This is equally true for viruses, rubella[4,125], bacteria, animal parasites including toxoplasma[33], spirochetes as well as fungi (Torula histolytica).

*Virus Diseases.* Among the virus diseases of the skin with neurologic involvement are herpes zoster and herpes

simplex. In reality, herpes zoster is primarily a disease of the ganglion, and the skin secondarily. Its usual manifestations are well known but recently certain phenomena have been recorded in the literature. These include association of zoster with monocytic leukemia[16a]; involvement of sensory nerves of the skin[39]; association with permanent paralysis of the phrenic nerve[60]; and involvement of the cranial nerves[32,42]. Cheatham[28] reported on the relation of heretofore unreported lesions in the pathogenesis of herpes zoster. He presented a case of herpes zoster with varicelliform eruption in which intranuclear inclusion bodies were demonstrated within the esophageal mucosa, myenteric plexus of the stomach, dorsal root ganglia, and a sympathetic ganglion at the level of the affected dorsal root ganglia. In addition, similar inclusions were seen within cells in lesions of the pancreas, adrenal glands and one ovary, associated with focal necrosis. It is postulated that the virus entered the body via the sympathetic nerves to the dorsal root ganglia, eventually reaching the skin by centrifugal spread along the respective peripheral nerves. The disseminated visceral and cutaneous lesions in this case resembled those described in varicella. The virus of herpes zoster and varicella are probably identical. This observation has by now had ample proof.

Herpes simplex infections have received considerable attention recently[89,118]. An outstanding compilation of infection with the virus of herpes simplex is that of Scott[109]. The mucocutaneous manifestations produced by the virus are: herpes simplex, eczema herpeticum, traumatic herpes, acute gingivostomatitis, recurrent stomatitis, herpes labialis, herpes progenitalis and vulvovaginitis. The central nervous system is subject to meningo-encephalitis. The eyes may also be affected and generalized infection may produce hepatitis in the newborn. Although herpes simplex virus has been known to produce fatal meningo-encephalitis, recent investigations indicate that there are cases which recover. In one series of cases, 7% were due to herpes[53]. Therefore, this antigen should be included in any diagnostic work-up.

*Cat-scratch Disease.* Cat-scratch disease is a newly recognized clinical entity of which hundreds of cases have been reported in America and Europe during the past 4 years. This infection follows a cat scratch or rarely some other form of skin injury. Within a few days an indolent primary lesion develops at the site of inoculation. Within the next few weeks striking regional lymphadenitis without intervening lymphangitis occurs. The nodes may be red and tender or relatively painless. Fever and systemic symptoms are usually present. Among these complications is encephalitis. The cutaneous manifestations may be erythema or maculopapular eruption, or erythema nodosum or multiforme. The nodes may regress spontaneously within a few weeks or proceed to suppuration with the development of bacteriologically sterile pus. Epstein[43b] who within one year 1945–46 saw four patients with cat-scratch fever, reported[43a] as para-anthrax since the viral nature of the condition was not recognized. Bacteriologic studies in Epstein's cases revealed a number of organisms, among them *B. anthracoides.* Daniels and MacMurray[36] who were among the first to report cases of cat-scratch disease in this country, state that as yet no definite organism has been isolated from these cases. An intradermal test has been developed. Clinically the process must be differentiated from tularemia, pyogenic infections, adenitis, infected cysts,

mononucleosis, lymphosarcoma, Hodgkin's disease, tuberculous adenitis, lymphogranuloma venereum and benign and malignant tumors.

*Meningococcemia.* According to Hill and Kinney[62], the presence of a cutaneous rash has always been recognized as one of the earliest and most reliable clinical signs of meningococcemia; a fact that has led clinicians in the past to employ such titles as malignant purpuric fever, petechial fever, black fever and spotted fever for these infections. Hill and Kinney studied 25 cases of fatal meningococcemia from the necropsy files of the Peter Bent Brigham, Boston Children's and Boston City Hospitals. The cutaneous lesions consisted of erythematous macules, papules, nodules, vesicles and petechial and purpuric lesions. Most patients exhibited combinations of the various types. Hemorrhagic and purpuric lesions were noted in the majority of cases. The cutaneous lesions of meningococcemia are the result of vascular damage which consists of endothelial damage, inflammation of the vessel wall, necrosis and thrombosis.

SARCOID OF BOECK. Sarcoidosis is a chronic, low-grade granulomatous process of unknown cause. There are signs and symptoms referable to involvement of one or more organs but the skin, lymph nodes, bones, lungs, eye and parotid gland are chiefly affected. The disease is associated with certain chemical changes in the blood (for example, elevation of the globulin), and certain roentgenographic changes in the lungs and bones. The tuberculin reaction is usually negative but patients with sarcoidosis are said to give positive reactions to the Kveim test (a not too reliable procedure).

Microscopically the lesions consist of naked tubercles with or without giant cells and usually without caseation. In this process, so much like tuberculosis and beryllosis[8a] in many respects, and even thought to be a tuberculous infection by some, it would be natural to expect neurological manifestations. Although the central nervous system is not a common site for lesions of this disease, Pennell[97] was able to collect 51 cases from the literature. In addition, 3 cases of manifestations of involvement of the central nervous system had been encountered at the Neurological Institute of New York. The occurrence of cerebrospinal fluid abnormalities in 2 of these 3 cases lend additional presumptive evidence, according to Pennell, as to the nature of the disease. The peripheral nervous system is more commonly involved than is the central nervous system. The peripheral nerve manifestations include: reflex changes, sensory loss and cranial nerve palsies (especially Bell's palsy, but the optic nerve, eighth, ninth and tenth nerves have also been affected). In patients with necropsy evidence of central nervous system involvement, lesions have occurred in the pituitary gland, hypothalmus, optic nerves and chiasm, the dura, the tentorium, the retina and the brain meninges. Clinical symptoms and signs of involvement of the central nervous system were varied: headaches, visual complaints, confusional states, various motor and sensory defects, generalized seizures, hemiplegia and cerebral signs. Ocular signs were especially prominent: papilledema, visual defects. Everts[45] reported a patient with symptoms of increased intracranial pressure and homonymous hemianopsia. A large sarcoid tumor of the occipital lobe was observed at operation. Four years later the patient was examined because of sarcoid lesions of the skin and the spinal fluid was found to be abnormal. Pituitary and hypothalmus lesions were prominent: diabetes insipidus, adiposogenital syndrome and pituitary edema.

It would appear that the lesions of Boeck's sarcoid have been found in almost every part of the nervous system and vary from chronic meningeal lesions to actual tumor-like masses. The pituitary gland is especially susceptible and Pennell found that 35% of the reported patients presented symptoms of diabetes insipidus sometime during the course of their disease. Pennell believes that the occurrence of low cerebrospinal fluid sugar is additional evidence that Boeck's sarcoid is caused by an infectious agent. Whether this conclusion is valid or not is subject to much discussion. The neurologic status of Boeck's sarcoid has been discussed at length in various publications[8a]. Hoök[65] reported 9 patients in 7 of whom neurological symptoms were the initial complaint.

ALLERGY. While we might yield to the idea that allergic reactions may be affected by psychic influence (see below), neurologic factors would hardly be considered seriously in allergy. Yet certain data have been accumulated suggesting that the nervous system may participate in allergic sensitization phenomena[11,48,70,95,131b,138b]. Bereston studied certain effects of central nervous system lesions upon cutaneous allergic reactions. He found that in paraplegic individuals the reactions to epidermal patch tests, to intradermal histamine and acetylcholine injections, and intracutaneous trichophytin and tuberculin tests, are diminished in a high percentage of cases, probably due to nerve degeneration. In hemiplegic individuals there is no altered response to tuberculin, trichophytin, histamine and acetylcholine injections in the skin of the affected side, but a diminished reaction to patch test with simple chemicals such as 1, 2, 4-dinitrochlorobenzene. In sharp contrast to these results, reactions to ultraviolet light tend to be stronger in the affected skin sites in both hemiplegics and paraplegics. No explanation can be given at present for this difference. Most clinicians are familiar with localized edema of the brain on the basis of food or other allergy in conjunction with angioneurotic edema. This phenomenon was stressed by Rowe[106]. Zeller[144] found abnormalities in the electroencephalograms of a group of patients with hay fever, asthma, urticaria or vasomotor rhinitis. These waves were not characteristic of allergy. They indicate a higher incidence in allergic persons than in non-allergic individuals.

CERTAIN NEUROLOGIC DISEASES WITH CUTANEOUS LESIONS. *Trophoneuroses.* The occurrence of unilateral dermatitis of the face in patients after removal of the gasserian ganglion are well known[121]. Recently, Bloom[15] has collected information on cutaneous ulceration in organic central nervous system disease. The clinical types of trophic ulcers include malum perforans which is most commonly seen in tabes dorsalis, trophic ulcers of the nostrils seen in encephalitis lethargica, as well as in tabes dorsalis, and decubitus ulcers. These different types of trophic ulcers seen in association with disease and injury of the central nervous system have essentially the same pathogenesis. Their different clinical features are determined chiefly by difference in location of the cutaneous lesion and somewhat by the kind of underlying nervous system disease.

*Vesicular Lesions in Cases of Coma.* Olsen[94] points out that, when vesicular lesions of the skin develop in unconscious patients, the possibility of thermal burns is naturally considered, and in cases such as intoxication, asphyxiation, and anesthesia or deep sedation, suspicion of negligence may arise. In acutely ill patients who are unconscious, an unusual susceptibility to

breaking down of the skin in pressure areas is sometimes said to be the result of nerve injuries. This theory cannot be refuted. In coma there is unrelieved pressure on the skin due to immobility. Furthermore, respiration and circulation are depressed, and in some cases residual neuritis is found after the patient regains consciousness. Blisters resulting from pressure are second degree decubitus lesions, which in the terminology of burns fall between erythema (wheals or welts) and deep necrosis. In the same patient in whom blisters are found, the surface of skin may also show wheals and ulcers, but the vesicles and bullae most strongly suggest burns such as may be attributed to heating pads, hot water bottles, moist heat applications, infra-red light therapy or diathermy. Olsen cites several case histories to illustrate that the nature of vesicular lesions developing during coma and the responsibility for their occurrence may assume medicolegal interest. He emphasizes that they are "second degree" decubitus lesions. They are not pathognomonic of any one kind of coma, but are seen in carbon monoxide poisoning, asphyxia with natural gas, barbiturate intoxication, and spinal anesthesia.

*Cushing's Syndrome.* Mali[86] reported two patients with a peculiar atrophy with pigmentation of the "forelegs." The lesions in both cases were presumed to be of pituitary origin. These were present in addition to the usual cutaneous manifestations (for example, striae distensae). Curth[34] in a letter to the Editor regarding Rothman's[105c] case of pituitary basophilism in the juvenile type of acanthosis nigricans maintains that "up to the present time, however, the etiological significance of the pituitary gland in acanthosis nigricans has not been conclusively shown."

*Poliomyelitis.* Poliomyelitis, according to Reyes[102] is frequently associated with hyperkeratinization. He felt that 98% of 84 children suffering from poliomyelitis had skin lesions located on both infrapatellar regions, on the anterior and lateral aspects of both ankle joints, on the dorsa of both feet, on soles and on the malleoli. He attributed these lesions to vitamin A deficiency.

PSYCHONEUROGENOUS COMPONENT OF CUTANEOUS REACTION MECHANISM. In 1939–1940, Stokes, Beerman and Ingraham[121] reviewed the available literature on "cutaneous neuropsychiatry." This survey included discussions of the vascular and vasculo-visceral fields; the sweat mechanism; the gastrointestinal mechanism; direct neural and neurovascular mechanisms (The Lewis-Dale Concept); metabolic studies; studies of the pruritus mechanism; central (thalamic and other) mechanisms; skin infections conditioned by psychoneurogenous elements; allergic and psychoneurogenous correlation in the skin and a detailed list of cutaneous diseases in which the psychoneurogenous components had been clearly recognized. Stokes and Beerman[120] then elaborated on one of the facets in this list: Psychosomatic Correlations in Allergic Conditions. In this study evidence of the psychosomatic factor in allergy is correlated. Urbach[131a] collated the literature bearing on this subject to 1946. He too found evidence not only for the psychoneurogenous background of some allergic processes but also certain limitation of the psychosomatic approach to allergy. Wittkower and Russell[138] without denying "the extreme specificity and absence of any element of suggestion in many examples of allergic reaction," insist that "careful search for an allergen should be accompanied by equally careful enquiries into the patient's personality and emotional life circumstances at the time of the allergic episodes."

On the other hand, O'Leary[93] stated

that, "It appears to me that the psychosomatic features of the atopic are a part of and not the cause of the atopy. I have not been impressed with psychoanalysis or profound psychotherapy as therapeutic agents, even by those well experienced in such procedures."

Macalpine[84d], in her scholarly and critical evaluation of psychosomatic medicine in relation to dermatology, felt that "urticaria and angioneurotic edema are in many cases without doubt found to have a psychic origin. The same applies to some cases presenting as contact dermatitis, allergic conditions, light sensitivity, hyperhidrosis and pompholyx, and certain pruriginous eczemas, pruritus vulvae and pruritus ani."

These divergent viewpoints in regard to the psychoneurogenous factor in such easily observed processes as allergic states, affect the general attitudes toward the general problem in the literature. Since this has been so extensively and well reviewed in a great many studies, cataloguing of some of the recent sources is all that is possible in the brief space allotted here. As Macalpine so aptly stated, "to report individual results and findings without comment is to add to the confusion already existing particularly as much of the literature is of a tentative and speculative nature, although frequently presented as factual." Among these recent sources of information are the aforementioned volume by Wittkower and Russell, and the critical review by Macalpine. Macalpine has also produced a number of other contributions on specific topics: facial dermatoses[84c]; pruritus ani[84b]; psychosomatic symptom formation[84a]; and the application of psychology to dermatoses[85]. Cormia[31] has discussed the basic concepts in the production and management of the psychosomatic dermatoses. Allington[2] has reviewed the psychotherapy of warts. Frumess[52] has assessed the role of emotions in dermatoses. Shaffer and Beerman[112] discussed certain psychodynamic mechanisms and clinical and histopathologic correlations of lichen simplex chronicus and its variants. Seitz[111] in one of his many excellent contributions, has attempted to approach psychocutaneous problems from an experimental angle. Klauder[74] a pioneer in this field, long ago compiled a paper which still makes good reading. The cudgels in behalf of psychosomatic factors in dermatology have been recently taken up by Wright[139] and by English[41]. Brunner[22] has attempted to define a biologic basis of psychosomatic diseases of the skin. Silverman[116] has also presented a brief summary of some of these problems. Delusions of parasitosis are reviewed by Aleshire[1]. The psychological implications of tattooing were reviewed briefly by Beerman and Lane[9].

SYNDROMES OF MULTIPLE ABNORMAL GROWTHS OF THE CENTRAL NERVOUS SYSTEM AND OTHER ORGANS. There are a number of diseases consisting of multiple abnormal growths of the central nervous system and other organs, especially the skin. The best studied of these is tuberous sclerosis.

*Diseases of the Skin in Feeble-minded Persons.* The incidence of diseases of the skin in the feeble-minded has been investigated by Butterworth and Wilson[23b]. At the Pennhurst State School for the Feeble-Minded, 1,895 patients of whom 1,062 (56%) were male and 833 (44%) female were examined in the Spring of 1935. Ninety-six and eight-tenths per cent of the patients were white. Seventy-two per cent of them were between the ages of 10 and 30 years, the distribution being: first decade, 7%; second decade, 42%; third decade, 30%; fourth decade, 15%; fifth decade, 4%; sixth decade, 1%; beyond sixth decade, 1%. The most com-

mon cutaneous diseases found were: 152 cases of acne vulgaris; 140 with nevi; 63 with tinea; 53 with pyoderma; 39 with striae distensae; 30 with dermatitis traumatica; 20 with verrucae; 17 with hypertrichosis; 16 with perleche and 16 with molluscum contagiosum. There were 780 dermatologic diagnoses made in 654 cases. The incidence of cutaneous disease and abnormalities was about equal in both sexes. Five cases of neurofibromatosis were noted and 6 epileptics with adenoma sebaceum were included in this series of patients. The encephalotrigeminal syndrome was definitely proved in one case and was probably present in 20 others. Scrotal tongue was common. Vasomotor changes, while frequently noted, were not classified. Numerous stigmata likewise frequently noted were not analyzed.

*Cutis Verticis Gyrata.* The unusual conformation of the scalp called by a variety of descriptive names (for example, "bulldog scalp") has been reviewed by Polan and Butterworth[100]. They also added 7 new cases. Cutis verticis gyrata has been known since 1843 and has been the subject of a number of discussions but not until 1906 was it brought to the attention of dermatologists. In the literature prior to 1952, Polan and Butterworth found 275 cases of the process. Of those with data, males predominated by a ratio of 5.6 to 1. The abnormality was discovered only accidentally in most cases. In 13 of 275 cases there was a familial occurrence. Polan and Butterworth's cases were observed during the 17 years prior to 1953, at the Pennhurst State School for the Feeble-Minded.

In cutis verticis gyrata, the surface of the scalp is thrown into elevated folds between which there are furrows or grooves. The area involved may vary from a small localized patch to the entire scalp. The vertex and occiput have been most frequently involved. The hair is usually dark in color. The mobility of the scalp and the color of the skin are usually unaffected. Abortive cases may occur.

Of the reported cases 28.4% manifested evidence of a neuropathic diathesis. Of the neuropathic group, 20 were insane, 25 were mentally defective, 26 were suffering from "idiocy and schizophrenia," 6 were epileptic and mentally defective, and one was epileptic. This association of cutis verticis gyrata with lunacy, defective mentality or epilepsy appears to be more than a matter of chance. Six of Polan and Butterworth's 7 new cases occurred in mentally and physically defective individuals. Cutis verticis gyrata is not a disease entity but rather either an anomaly of development sometimes associated with other evidence of constitutional inferiority or a manifestation of some other preceding or underlying pathological condition. Polan and Butterworth have accordingly classified the cases as "primary" and "secondary." Of the reported cases, 48% were of the primary type and 52% were of secondary character. Treatment consists of removal of the underlying process in cases of secondary type and extirpation by a variety of methods of the affected part of the scalp, followed by any necessary plastic procedure in occasional cases.

*Neurocutaneous Syndromes, (Congenital Ectodermoses: Phakomatoses).* As previously mentioned, neurologists are more familiar with bizarre neurologic symptoms and signs occurring in association with nevoid changes in the skin. Yakovlev and Guthrie[140], more than 20 years ago, attempted to classify these heterogenous syndromes. They proposed three main groups: (1) von Recklinghausen's neurofibromatosis; (2) Bourneville's tuberous sclerosis and (3) the encephalo-trigeminal vascular

syndrome (angiomatosis of the brain associated with cutaneous nevi in the area of trigeminal distribution).

In 1923, Van der Hoeve[133a] proposed the term "phakomatoses" to describe neurofibromatosis and tuberous sclerosis. In 1932, he[133b] extended the term to include von Hippel-Lindau disease and, in 1937, Van der Hoeve, Brouwer and Mahoney[20] added the Sturge-Weber syndrome to the group. There are now four different processes in the phakomatosis group: (1) tuberous sclerosis (Bourneville's disease); (2) neurofibromatosis (von Recklinghausen's disease); (3) Angiomatosis retinae et cerebelli (von Hippel-Lindau disease); and (4) nevus flammeus and glaucoma (Sturge-Weber syndrome). Since Kirby[72] has so recently described these processes, we will only point out certain features.

Von Recklinghausen's disease is a well known process, the chief manifestations of which consist of neurofibromatous tumors in the skin and along peripheral nerve trunks and café au lait spots. The association of multiple neurofibromatosis with lowered mentality has long been observed but it is often seen in patients with normal mentality. Anomalies of bone, ocular manifestations and other developmental abnormalities may occur. Incomplete forms of this process are often seen. Thannhauser[128] has pointed out in his extensive study of this condition that neurofibromatosis and osteitis fibrosa cystica localisata et disseminata have a common pathogenesis. Inglis[66] has advanced the hypothesis that it is not neurofibromatosis as such that is inherited but the predisposition to neurofibromatosis, a predisposition which is thought to be wide in its application and to influence the development of a great variety of lesions at the basic intrinsic factor level, a less varied group of lesions at the neural intrinsic factor level, and a still more restricted group of lesions at the neurofibromatosis level. Intrinsic factors may play a part in the causation of certain examples of a variety of conditions which occur in patients or their close relatives who, though free from neurofibromata, have one or more lesions belonging to the neurofibromatosis complex. Borberg[18] concluded from the literature and his personal observations that tuberous sclerosis and von Recklinghausen's disease are related developmental anomalies which explains the common features of manifestation, but nevertheless they are unusually independent diseases due to two different genes. Kirby in his review has encountered examples of mixed tuberous sclerosis and neurofibromatosis.

McNairy and Montgomery[87] found nerve fibers in 12 of 15 examples of the cutaneous lesions of neurofibromatosis. This indicates that the lesions are true neurofibromas.

Tuberous sclerosis (Bourneville's disease epiloia) first recognized by Bourneville, in 1880[19], has received much attention in the literature of dermatology, ophthalmology and neurology. It consists essentially of mental deficiency, epilepsy and adenoma sebaceum. The term tuberous refers to the "potato-like" appearance of the diseased foci in the cortex of the cerebral hemisphere. The dermatologic manifestations of this process have been well described by Butterworth and Wilson[23b]. Based on 10 cases, Butterworth found no sexual differences but did observe hereditary and familial features. The dermatologic lesions consisted of:

1. Hyperplasias and tumors
   - A. Adenoma sebaceum
     1. Papular variety
     2. Plaque or nevoid variety
   - B. Fibrous hyperplasias
     1. Polypi; cutaneous tags

2. Miliary fibrous tubercles
3. Raised subcutaneous or intracutaneous; fibromas of the scalp
4. Collagenous Plaques
   (*a*) Shagreen patches
   (*b*) Purplish red plaques
   (*c*) Goose flesh patches
   (*d*) Pigskin patches
   (*e*) Yellowish cauliflower-like patches
5. Subungual and periungual fibromas
6. Gingival, lingual and palatal fibromas

C. Tumors
1. Lipomas
2. Fibromyolipoma
3. Angiofibrolipoma
4. Syringocystadenoma

II. Nevi
1. Pigmented
2. Hairy
3. Vascular
4. Anemic

III. Disturbances of pigmentation
1. Café au lait "spots" or "macules"
2. Diffuse bronzing of extensive regions of the skin
3. Vitiligo and canities
4. Pale freckles

IV. Changes in the nails

V. Hyperkeratoses
1. Ichthyosis
2. Hereditary palmar and plantar keratoses

VI. Miscellaneous
1. Purpuric rash on the limbs and trunks
2. Generalized hypertrichosis
3. Warts
4. Macular atrophy

From the neurologic standpoint the more prominent feature of this disease is epilepsy. When present, it usually begins in the first two or three years of life. In addition, some cases may show focal signs, such as localized paresis and contractures, muscular spasms, clonus and defects in speech. Most of the patients are mental defectives. Catatonia and cerebellar signs may occur. Kirby reported that the ocular manifestations are more objective than subjective and the most significant finding is retinal tumor.

Von Hippel-Lindau disease (angiomatosis and arteriovenous communications in the retina) has been of great interest to ophthalmologists and neurologists. In 1947, both Kirby and Kinney and Fitzgerald[71] discussed the subject extensively. The latter group reported an example with hemangioblastoma of the spinal cord and syringomyelia.

Dermatologists are rather interested in the fourth category nevus flammeus and glaucoma (Sturge-Weber syndrome; Sturge-Weber-Dimitri syndrome; Weber-Dimitri disease; Sturge-Kalischer syndrome). In this process the nevus flammeus occurs in the distribution of one or all of the branches of the trigeminal nerve; convulsive seizures; hemiplegia, which is contralateral to the facial nerves, nevus; glaucoma; characteristic calcifications as evidenced by roentgenologic examination of the skull (appearing as sinuous, double contoured lines, with the convolutions of the cortex on the affected side) and mental retardation. The recent literature has been active in this field. Bluefarb[16b] reported a case with nearly all the classical features. Kirby described the ophthalmologic signs in detail. Chivo and Lindgren[29] studied 14 cases radiologically. The findings show typical calcification in 9, atypical in 3, and in 2 there was asymmetry of the skull with abnormal vascular channels in the vault and part of the lateral ventricles. There was also widening of the subarachnoid space. Lichtenstein and his colleagues[80,81] have been interested in this process for a long time. An abstract of the latest paper is a

good summary of this process, which he chooses to call Sturge-Weber-Dimitri syndrome. The clinical features of the Sturge-Weber-Dimitri syndrome are a vascular nevus of the face associated with signs of cerebral dysfunction, such as epilepsy, mental deficiency, and hemiplegia, and roentgenographic evidence of sinuous shadows within the skull. The skin lesion is usually a nevus flammeus of the face or scalp that often exhibits striking evidence of being confined to the areas of distribution of branches of the trigeminal nerve. It is usually unilateral but may be diffuse over both sides of the face, in which case the neural changes are often limited to the side more severely affected. Incomplete forms characterized by an absence either of visible cutaneous lesions or of evident brain disease have also been recognized. The Sturge-Weber-Dimitri syndrome is remarkable, not so much for the hemangiomatous dysplasia that constitutes its anatomical basis, as for the secondary changes in the brain that accompany it. The histopathological alterations discernible in the cerebral cortex underlying the intracranial hemangiomatosis, which is generally restricted to the leptomeninx, although minor foci may be found within the cerebral cortex and in the subcortical medullary substance, are of two distinct types: (1) complete or almost complete deficit of nerve cells with extensive gliosis and obliterative pericapillary fibrosis, and (2) pericapillary beading and sheathing, as well as spherical and mulberry concretions within the nerve cell layers with disorganization of the cytoarchitecture and gliosis. The changes in the cerebral cortex are probably caused by metabolic disturbances induced by venous stasis in the abnormally large number of pial veins. Very early development of extreme metabolic disturbances may result in complete loss of nerve cells with reactive gliosis and little calcification. A gradual reduction in metabolic activity, on the other hand, may lead to the deposition of either or both calcium and iron salts. The resulting double contour radiopaque densities visible in roentgenograms of patients with the Sturge-Weber-Dimitri syndrome will be found on close inspection to outline the cerebral convolutions, rather than calcified blood vessels. Similar lines of calcification appear in various other pathological states, but when they are demonstrated in the roentgenograms of persons with port wine nevi of the face, they permit positive identification of the Sturge-Weber-Dimitri syndrome.

## REFERENCES

(1) **Aleshire, I.:** J. Am. Med. Assn., **155,** 15, 1954. (2) **Allington, H. V.:** A.M.A. Arch. Dermat. & Syph., **66,** 316, 1952. (3) **Arnold, H. L.:** Internat. J. Leprosy, **16,** 335, 1948. (4) **Aycock, W. L.,** and **Ingalls, T. H.:** Am. J. Med. Sci., **212,** 366, 1946. (5) **Baló, J.,** and **Földvàri, F.:** Ann. Dermat. et Syph., **79,** 626, 1952. (6) **Bambridge, H.:** Pediatrics, **12,** 622, 1953. (7) **Bardach, M.:** Ztschr. Kinderh., **39,** 542, 1925. (8) **Beerman, H.:** (a) Am. J. Med. Sci., **221,** 462, 1951; (b) Med. Clin. N. America, **35,** 433, 1951. (9) **Beerman, H.,** and **Lane, R. A. G.:** Am. J. Med. Sci., **227,** 444, 1954. (10) **Behrman, H. T.,** and **Lee, K. K.:** A.M.A. Arch. Dermat. & Syph., **61,** 63, 1950. (11) **Bereston, E. S.:** J. Invest. Dermat., **6,** 75, 1945. (12) **Binkley, G. W.,** and **Johnson, H. H., Jr.:** A.M.A. Arch. Dermat. & Syph., **63,** 73, 1951. (13) **Black-Schaffer, B., Kambe, S., Furuta, M.,** and **Moloney, W. C.:** A.M.A. Am. J. Dis. Child., **87,** 737, 1954. (14) **Bloch, B.:** Schweiz. med. Wchnschr., **56,** 404, 1926. (15) **Bloom, D.:** New York State J. Med., **47,** 2425, 1947. (16) **Bluefarb, S. M.:** (a) A.M.A. Arch. Dermat. & Syph., **57,** 319, 1948; (b) Ibid., **59,** 531, 1949. (17) **Bogdasarian, R. M.,** and **Stout, A. P.:** A.M.A. Arch. Otolaryng., **38,** 62, 1943. (18)

**Borberg, A.**: Clinical and Genetic Investigations into Tuberous Sclerosis and Recklinghausen's Neurofibromatosis. Contribution to Elucidation of Interrelationship and Eugenics of the Syndromes. Copenhagen: Ejnar Munksgaard, 1951. (19) **Bourneville, D.**: Arch. de Neurol., **1**, 81, 1880–1881. (20) **Brouwer, B., Van der Hoeve, J.**, and **Mahoney, W.**: Verhand. Kon. Akad. van Wetenschappen, Amsterdam, **36**, 1, 1937. (21) **Bruce, G. M.**: Tr. Am. Ophthal. Soc., **38**, 149, 1940. (22) **Brunner, M. J.**: A.M.A. Arch. Dermat. & Syph., **57**, 374, 1948. (23) **Butterworth, T.**, and **Wilson, M. J.**: (a) Ibid., **43**, 1, 1941; (b) Ibid., **38**, 203, 1938.

(24) **Cammermeyer, J.**: A.M.A. Arch. Path., **42**, 1, 1946. (25) **Carney, R. G.**: A.M.A. Arch. Dermat. & Syph., **64**, 126, 1951. (26) **Caro, M. R.**, and **Senear, F. E.**: Ibid., **65**, 701, 1952. (27) **Chalmers, T. H.**, and **Keele, C. A.**: Brit. J. Dermat., **64**, 43, 1952. (28) **Cheatham, W. J.**: Am. J. Path., **29**, 401, 1953. (29) **Chivo, G. D.**, and **Lindgren, E.**: Acta radiol., **35**, 387, 1951. (30) **Cole, H. N., Jr., Irving, R. C., Lund, H. Z., Mercer, R. D.**, and **Schneider, R. W.**: A.M.A. Arch. Dermat. & Syph., **66**, 371, 1952. (31) **Cormia, F. E.**: Brit. J. Dermat., **63**, 83, 1951. (32) **Costello, M. J.**, and **Scott, M. J.**: A.M.A. Arch. Dermat. & Syph., **60**, 558, 1949. (33) **Cowen, D., Wolf, A.**, and **Paigo, B. H.**: A.M.A. Arch. Neurol. & Psychiat., **48**, 689, 1942. (34) **Curth, H. O.**: J. Am. Med. Assn., **157**, 266, 1955.

(35) **Dalsgaard-Nielsen, E.**, and **Dalsgaard-Nielsen, I.**: Ugesk. f. Laeger., **99**, 219, 1937. (36) **Daniels, W. B.**, and **MacMurray, F. G.**: J. Am. Med. Assn., **154**, 1247, 1954. (37) **Dixon, J. M.**: Am. J. Ophth., **34**, 1322, 1951. (38) **Doornink, F. J.**: Dermatologica, **102**, 63, 1951.

(39) **Ebert, M. H.**: A.M.A. Arch. Dermat. & Syph., **60**, 641, 1949. (40) **Edwards, E. A.**: New England J. Med., **250**, 710, 1954. (41) **English, O. S.**: A.M.A. Arch. Dermat. & Syph., **60**, 1063, 1949. (42) **Engström, H.**, and **Wohlfart, G.**: A.M.A. Arch. Neurol. & Psychiat., **62**, 638, 1949. (43) **Epstein, E.**: (a) A.M.A. Arch. Dermat. & Syph., **57**, 664, 1948; (b) Ibid., **66**, 240, 1952. (44) **Epstein, S., Vedder, J. S.**, and **Pinkus, H.**: Ibid., **65**, 557, 1952. (45) **Everts, W. H.**: Tr. Am. Neurol. Assn., **72**, 128, 1947, and personal communication to Pennell[97]. (46) **Ewing, G. M.**: Straub Clin. Proc., **20**, 25, 1954.

(47) **Featherston, W. M.**: J. Am. Med. Assn., **150**, 1006, 1952. (48) **Filipp, G.**: Hung. Med. Wkly., **95**, 25, 1954. (49) **Fitzpatrick, T. B.**, and **Lerner, A. B.**: A.M.A. Arch. Dermat. & Syph., **69**, 133, 1954. (50) **Flesch, P.**: in **Rothman, S.**: Physiology and Biochemistry of the Skin. Chicago: Univ. of Chicago Press, 1954. (51) **Frostig, J. P.**, and **Spies, T. D.**: Am. J. Med. Sci., **199**, 268, 1940. (52) **Frumess, G. M.**: J. Am. Med. Assn., **152**, 1417, 1953.

(53) **Gagliardi, B., Menghi, P.**, and **Rezza, E.**: Minerva pediat., **5**, 2, 1953. (54) **Gehman, J. R.**: Arch. Dis. Child., **19**, 1, 1944. (55) **Glaser, G. H.**: A.M.A. Arch. Neurol. & Psychiat., **67**, 745, 1952. (56) **Goltz, R. W.**, and **Laymon, C. W.**: A.M.A. Arch. Dermat. & Syph., **69**, 717, 1954. (57) **Guss, J. H.**: Virginia Med. Monthly, **74**, 454, 1947.

(58) **Haber, H.**: Brit. J. Dermat., **64**, 129, 1952. (59) **Haberlin, J. B.**, and **Garrard, H. F.**: A.M.A. Arch. Dermat. & Syph., **58**, 696, 1948. (60) **Halpern, S. L.**, and **Covner, A. H.**: A.M.A. Arch. Int. Med., **84**, 907, 1949. (61) **Haxthausen, H.**: Acta Derma-Vener., **27**, 352, 1947. (62) **Hill, W. R.**, and **Kinney, T. D.**: J. Am. Med. Assn., **134**, 513, 1947. (63) **Hitch, J. N.**: Ibid., **150**, 1004, 1952. (64) **Holm, E.**: Dansk. Med. Seelskab., **206**, 20, 1936–1937. (65) **Höök, O.**: A.M.A. Arch. Neurol. & Psychiat., **71**, 554, 1954.

(66) **Inglis, K.**: J. Path. & Bact., **62**, 519, 1950. (67) **Ito, M.**: (a) Nihon-Rinsho, **4**, 644, 1946; (b) Tohoku J. Exper. Med., **55**, (Suppl. 1), 1952.

(68) **Jessar, R. A., Lamont-Havers, R. W.**, and **Ragan, C.**: Ann. Int. Med., **38**, 717, 1953.

(69) **Kanee, B.**: A.M.A. Arch. Dermat. & Syph., **44**, 1086, 1944. (70) **Karnosh, L. J.**: Psychiat. Quart., **18**, 618 1944. (71) **Kinney, T. D.**, and **Fitzgerald, P. J.**: A.M.A. Arch. Path., **43**, 439, 1947. (72) **Kirby, T. J.**: Am. J. Med. Sci., **222**, 227, 1951. (73) **Kitamura, K., Fukushiro, R.**, and **Miyabayashi, T.**: A.M.A. Arch. Dermat. & Syph., **69**, 667, 1954. (74) **Klauder, J. V.**: J. Nerv. & Ment. Dis., **84**, 249, 1936. (75) **Kuno**: Cited by **Chalmers and Keele**[27].

(76) **Leavitt, H. C.**: Neurology, **3**, 800, 1953. (77) **Leinwant, I., Duryee, A. W.**, and **Richter, M. N.**: Ann. Int. Med., **41**, 1003, 1954. (78) **Lerner, A. B., Shizume, K.**, and **Fitzpatrick, T. B.**: J. Invest. Dermat., **21**, 337, 1953. (79) **Lewis, B. I., Sinton,**

**D. W.**, and **Knott, J. R.**: A.M.A. Arch. Int. Med., **93**, 315, 1954. (**80**) **Lichtenstein, B. W.**: A.M.A. Arch. Neurol. & Psychiat., **71**, 291, 1954. (**81**) **Lichtenstein, B. W.**, and **Rosenberg, C.**: J. Neuropath. & Exper. Neurol., **6**, 369, 1941. (**82**) **Lockwood, J. H.**: Urol. & Cutan. Rev., **53**, 400, 1949. (**83**) **Loveman, A. B., Fliegelman, M. T., Weidman, A. I.**, and **Rein, C. R.**: J. Pediat., **40**, 442, 1952.

(84) **Macalpine, I.**: (a) Lancet, **1**, 278, 1952; (b) Psychosom. Med., **15**, 499, 1953; (c) Brit. J. Dermat., **63**, 177, 1953; (d) A Critical Evaluation of Psychosomatic Medicine in Relation to Dermatology, in Modern Trends in Dermatology by **R. M. B. MacKenna**. New York: P. B. Hoeber, 1954, p. 18. (**85**) **MacKenna, R. M. B.**, and **Macalpine, I.**: Lancet, **1**, 65, 1951. (**86**) **Mali, J. W. H.**: Dermatologica, **101**, 33, 1950. (**87**) **McNairy, D. J.**, and **Montgomery, H.**: A.M.A. Arch. Dermat. & Syph., **51**, 384, 1945. (**88**) **Miescher, G.**, and **Schönberg, A.**: Bull. Schweiz. Akad. d. med. Wissensch., **1**, 101, 1944. (**89**) **Miller, O. B., Arbesman, C.**, and **Baer, R. L.**: A.M.A. Arch. Dermat. & Syph., **62**, 477, 1950. (**90**) **Montgomery, H.**, and **O'Leary, P. A.**: Ibid., **29**, 26, 1934.

(91) **Neill, K. G.**: Brit. Med. J., **2**, 320, 1953. (**92**) **Netsky, M. G.**, and **Stars, H.**: Res. Publ. Assn. Nerv. & Ment. Dis., **27**, 610, 1948.

(93) **O'Leary, P. A.**: South. Med. J., **46**, 67, 1953. (**94**) **Olsen, C. W.**: J. Nerv. & Ment. Dis., **118**, 412, 1953. (**95**) **Ormea, F.**, and **Zino, G.**: Minerva dermat., **28**, 26, 1953.

(96) **Pardo-Castello, V., Tiant, F. R.**, and **Pineyro, R.**: A.M.A. Arch. Dermat. & Syph., **55**, 783, 1947. (**97**) **Pennell, W. H.**: A.M.A. Arch. Neurol. & Psychiat., **66**, 728, 1951. (**98**) **Philpott, J. A., Jr., Philpott, O. S.**, and **Woodburne, A. R.**: in press, 1954. (**99**) **Pier, P. G.**: J. Am. Med. Assn., **153**, 216, 1953. (**100**) **Polan, S.**, and **Butterworth, T.**: Am. J. Ment. Deficiency, **57**, 613, 1953. (**101**) **Prichard, R. W.**, and **Custer, R. P.**: Cancer, **5**, 297, 1952.

(102) **Reyes, J. G.**: New York State J. Med., **45**, 1673, 1945. (**103**) **Robinson, S. S.**, and **Tasker, S.**: Urol. & Cutan. Rev., **52**, 467, 1948. (**104**) **Ronchese, F.**: A.M.A. Arch. Dermat. & Syph., **28**, 639, 1933. (**105**) **Rothman, S.**: (a) Psychosom. Med., **7**, 90, 1945; (b) Physiology and Biochemistry of the Skin. Chicago: Univ. of Chicago Press, 1954; (c) J. Am. Med. Assn., **156**, 242, 1954. (**106**) **Rowe, A. H.**: J. Nerv. & Ment. Dis., **99**, 834, 1944. (**107**) **Rubin, L.**: A.M.A. Arch. Dermat. & Syph., **58**, 1, 1948. (**108**) **Russell, P. W., Haserick, J. R.**, and **Zucker, E. M.**: A.M.A. Arch. Int. Med., **88**, 78, 1951.

(109) **Scott, T. F. McN.**: New England J. Med., **250**, 183, 1954. (**110**) **Sedgwick, R. P.**, and **Von Hagen, K. O.**: Bull. Los Angeles Neurol. Assn., **13**, 129, 1948. (**111**) **Seitz, P. F. D.**: J. Invest. Dermat., **13**, 199, 1949. (**112**) **Shaffer, B.**, and **Beerman, H.**: A.M.A. Arch. Dermat. & Syph., **64**, 340, 1951. (**113**) **Shelley, W. B., Horvath, P. N.**, and **Pillsbury, D. M.**: Medicine, **29**, 195, 1950. (**114**) **Shizume, K., Lerner, A. B.**, and **Fitzpatrick, T. B.**: Endocrinology, **54**, 553, 1954. (**115**) **Siemens**: Cited by **Doornink**[38]. (**116**) **Silverman, A. J.**: Am. J. Med. Sci., **226**, 104, 1953. (**117**) **Sjögren, H.**: Acta ophthal., Supp. 2, p. 1, 1933. (**118**) **Slavin, H. B.**: Med. Clin. N. America, **35**, 563, 1951. (**119**) **Stevens, F. A.**: J. Am. Med. Assn., **156**, 223, 1954. (**120**) **Stokes, J. H.**, and **Beerman, H.**: Psychosom. Med., **2**, 438, 1940. (**121**) **Stokes, J. H., Beerman, H.**, and **Ingraham, N. R.**: Am. J. Med. Sci., **198**, 577, 1939 and **200**, 560, 1940. (**122**) **Stout, A. P.**: Am. J. Cancer, **24**, 751, 1935. (**123**) **Sulzberger, M. B.**: Arch. f. Dermat. u. Syph., **154**, 19, 1928. (**124**) **Sulzberger, M. B.**, and **Baer, R. L.**: Year Book of Dermatology & Syphilology. Chicago: The Year Book Publishers, Inc., 1953-1954. (**125**) **Swan, C.**, and **Tosterin, A. L.**: Med. J. Australia, **1**, 645, 1946. (**126**) **Szymanski, F. J.**, and **Caro, R.**: Read at Am. Med. Assn., June, 1954.

(127) **Taylor, R. M.**, and **Pacella, B. L.**: J. Nerv. & Ment. Dis., **109**, 42, 1949. (**128**) **Thannhauser, S. J.**: Medicine, **23**, 105, 1944. (**129**) **Tumulty, P. A.**: J. Am. Med. Assn., **156**, 947, 1954.

(130) **Upshaw, B. Y.**, and **Montgomery, H.**: A.M.A. Arch. Dermat. & Syph., **69**, 1170, 1949. (**131**) **Urbach, E.**: (a) Progress in Neurology and Psychiatry. New York: Grune & Stratton, Inc., 1946, p. 336; (b) Skin Diseases, Nutrition and Metabolism. New York: Grune & Stratton, Inc., 1946. (**132**) **Urbach, E.**, and **Wolfram, S.**: Arch. f. Dermat. u. Syph., **176**, 167, 1938..

(133) **Van der Hoeve, J.**: (a) Tr. Ophth. Soc. U. Kingdom, **43**, 534, 1923; (b) Ibid., **52**, 380, 1932.

(134) **Washington, J. A.:** Cited by **Cole, H. N., Jr., Irving, R. C., Lund, H. Z., Mercer, R. D.,** and **Schneider, R. W.**[30]. (135) **Wheeler, C. E., Cawley, E. P., Gray, H. T.,** and **Curtis, A. C.:** A.M.A. Arch. Dermat. & Syph., **68,** 685, 1953. (136) **Williams, H. L.:** Ann. Otol., Rhinol. & Laryngol., **60,** 122, 1951. (137) **Wilson, J. W., Levitt, H., Harris, T. L.,** and **Heiligman, E. M.:** J. Am. Med. Assn., **150,** 1002, 1952. (138) **Wittkower, E.,** and **Russell, B.:** (a) Emotional Factors in Skin Diseases. New York: P. B. Hoeber, 1953; (b) J. Allergy, **23,** 76, 1952. (139) **Wright, C. S.:** South. Med. J., **42,** 951, 1949.

(140) **Yakovlev, P. E.,** and **Guthrie, R. H.:** A.M.A. Arch. Neurol. & Psychiat., **26,** 1145, 1931. (141) **Yannett, H.,** and **Lieberman, R.:** J. Am. Med. Assn., **130,** 335, 1946.

(142) **Zak, F. G.:** Brit. J. Dermat., **62,** 351, 1950. (143) **Zeligman, I.,** and **Scalia, S. P.:** A.M.A. Arch. Dermat. & Syph., **69,** 342, 1954. (144) **Zeller, M.:** Cited by **Urbach, E.**[119]. (145) **Zimmerman, H. M.,** and **Yannett, A.:** A.M.A. Am. J. Dis. Child., **49,** 418, 1935.

# PHYSIOLOGY

PROCEEDINGS OF

## The Physiological Society of Philadelphia

SESSION OF APRIL 19, 1955

**Radiant Heat Load on Man in the Arctic.** H. T. HAMMEL, PH.D., J. D. HARDY, PH.D., and A. M. STOLL, PH.D. (Department of Physiology, University of Pennsylvania, and Naval Air Development Center, Johnsville, Pa.) The radiant heat load on man in interior Alaska in the absence of direct solar radiation is dependent upon the radiant temperature of the sky. The radiant sky temperature measured at the earth's surface with a directional radiometer is little affected by ice fog and is only a few degrees lower at night than in day, even though the surface air temperature may be unchanged. The water content of the atmosphere, on the other hand, strongly affects the radiant sky temperature. Cloud cover equates radiant temperature to the base temperature of the cloud mass. Depending upon the density of haze and of invisible vapor the radiant sky temperature ranges from 10° C. to 50° C. below the air temperature at the surface. During summer observations the radiant temperatures ranged from +20° to −20° C. During winter the range extended from −15° C. to −75° C. Radiant temperatures measured at 40,000 ft. from an aircraft were highly variable, ranging from −70° C. to −125° C. More than 99% of the water content of the atmosphere was below 40,000 ft.; still the trace of water remaining was absorbing strongly in the far infra-red. Uneven distribution of the trace amounts of water vapor and haze particles may account for the high variability in the radiant sky temperature at high altitude over an area of 75 miles' radius.

**Effect of Some Anesthetic Agents on Myocardial Function.** HENRY L. PRICE, M.D., and MARTIN HELRICH, M.D. (Department of Anesthesiology, Hospital of the University of Pennsylvania.) Recent observations in man have shown that the level of intrathoracic venous pressure is often greatly elevated (10 to 15 cm. $H_2O$) during anesthesia with cyclopropane, moderately increased with diethyl ether, but little altered during thiopental anesthesia. Since these observations could be explained if the anesthetic agents exerted quantitatively different effects on myocardial contractility, these effects were measured in the dog heart-lung preparation of Knowlton and Starling.

Forty-one preparations were studied. The anesthetic agents tested were cyclopropane, diethyl ether, nitrous oxide and thiopental sodium. After the control measurements were completed, cyclopropane and nitrous oxide were administered from a Tissot spirometer through a Palmer pump. Diethyl ether and thiopental were added directly to the blood reservoir. When equilibration between blood and tissues was sufficiently complete (90 to 95%) function measurements were repeated. After this, cyclopropane, diethyl ether, and nitrous oxide were removed by ventilation with oxygen or room air (room air used for ventilation during control periods when the percentage of oxygen in the test mixture was between 20 and 40%; oxygen concentrations less than 20% were not used). Myocardial

contractility was expressed quantitatively as the slope of the line relating the rate of aortic blood flow and the level of right atrial pressure; the blood flow was caused to vary between 0.3 and 1 to 2 liters per minute by raising and lowering the blood reservoir. Spontaneous failure of the preparations made it necessary to draw smooth curves through the control points in order to estimate the level of functional ability to be expected during the test period. In the case of thiopental, the control points were extrapolated to determine the expected response.

Each of the substances tested depressed myocardial contractility at blood concentrations less than those necessary for anesthesia in the intact animal. At blood concentrations producing approximately equal depth of general anesthesia, the depression of the dog myocardium by the four substances was similar, although thiopental had somewhat less effect than the other agents.

**The Use of Strontium for Investigating Ionic Mechanisms in Heart Muscle.** LYELL J. THOMAS, JR., PH.D., (Dept. of Pharmacology, Woman's Medical College, Philadelphia, Pa.). $Sr^{++}$, the ion most similar physiologically to $Ca^{++}$, has been used for investigating the mechanisms of action of $Ca^{++}$, $K^{+}$, and digitalis on the isolated, perfused frog heart. It was found that hearts perfused with a $Sr^{++}$ Ringer solution (1.0 mM./L. $Sr^{++}$ substituted for $Ca^{++}$) will beat autonomously for as long as 6 hours. However, flame photometer analyses involving 44 frog heart ventricles showed that $Sr^{++}$ perfused hearts suffer a 25% to 30% loss of $K^{+}$ with an equivalent gain in $Na^{+}$ in 3 hours. This is not increased by perfusion for 5½ hours. These $K^{+}$-$Na^{+}$ changes do not occur in a $Ca^{++}$ Ringer (1.0 mM./L. $Ca^{++}$) nor in a Ringer containing 0.8 mM./L.$Sr^{++}$ with 0.2 mM./L. $Ca^{++}$. The contractile pattern of the electrically driven heart has been analyzed using the isometric technique of Hajdu and Szent Gyorgyi, modified to permit a continuous flow of perfusate through the heart. When perfused with a $Ca^{++}$ Ringer, the heart responds to the absence of $K^{+}$ with increased contractile force and prolonged systole, whereas the readdition of $K^{+}$ (2.5 mM./L.) reduces the contractile force and shortens the systole. However, the contractile pattern of a $Sr^{++}$ perfused heart is but little affected by the presence or absence of $K^{+}$ from the Ringer and resembles that of a $Ca^{++}$ perfused heart in a low $K^{+}$ Ringer. The addition of as little as 0.01 mM./L. $Ca^{++}$ partially restores the reactivity of the $Sr^{++}$ perfused heart to $K^{+}$ and shortens the systole. Addition of a larger amount of $Ca^{++}$ (0.1 mM./L.) produces a depression of contractile force which follows an exponential time course with ½ maximum depression occurring in 1 to 3 minutes. The amount of depression is much greater for a hypodynamic heart than for a fresh heart. This depressant action of $Ca^{++}$ in a $Sr^{++}$ Ringer is not affected by atropine but is altered by digitalis. Digitalization reduces the amount of depression but increases the rate at which maximum depression is attained. These results suggest a dual action of $Ca^{++}$ on the heart. The well known inotropic action of $Ca^{++}$ on contractile force is produced to about the same degree by $Sr^{++}$. However, $Ca^{++}$ appears to have an additional action related to the maintainance of intracellular $K^{+}$ and to the ability of the muscle fiber to relax. As judged by the contractile response of the $Sr^{++}$ perfused heart to $Ca^{++}$, the site of this action appears to have a higher affinity for $Ca^{++}$ than for $Sr^{++}$. Also, the affinity of this site for $Ca^{++}$ appears to change with the condition

of the heart and with digitalization. Preliminary experiments with $Ca^{45}$ have shown that $Ca^{++}$ is bound selectively by the heart in the presence of excess $Sr^{++}$. The effect of the hypodynamic condition and of digitalization on $Ca^{++}$-$Sr^{++}$ uptake by the frog heart is being investigated at the present time.

**Direct Microscopic Observation of the Lung Circulation in Spontaneously Breathing Cats.** JOHNSON S. L. LING, M.S., PH.D. (Department of Pharmacology, University of Pennsylvania). A method for direct microscopic observation of the lung circulation in spontaneously breathing cats has been developed. The cat is anesthetized with Dial-Urethane, 0.6 cc. per kg. b.w., injected peritoneally. The cat selected should be young and thin; the lung apex in such a cat is enclosed in a tight-fitting pleural pocket lying well-exposed above the border of the first rib. The animal is stretched out on a cat board and tied with head and chest facing upwards. After shaving the areas over the trachea and left upper lobe lung apex, the trachea is cut open and connected to a tracheal cannula provided with inspiratory and expiratory water valves. A careful incision is made along the first rib on the left thoracic wall from the sternum laterally to a region where the left fore-limb attaches to the thorax. Care should be taken that the rib is not touched by the scalpel, for bleeding from the rib can later obscure the pleural window. The cut portions of skin and muscles are then pulled apart. The sternocleidomastoid muscle, which remains, is then severed and reflected. The top layers of cells of the parietal pleura are carefully removed with fine forceps until the pleural window becomes sufficiently transparent to permit microscopic observations of the tiniest blood vessels lying within the lung apex to be made. The illuminating system consists of a 4.5 ampere carbon arc lamp which sends a beam of light through a solution of copper sulphate-picric acid onto a magnifying lens. This lens condenses the light rays onto one end of a well-polished plexiglass rod. The curved tip of the rod is carefully inserted into the mediastinal space and placed beneath the undersurface of the left upper lobe lung apex, for transillumination. Since the thoracic pleura remains unbroken, the negative intrathoracic pressure has not been altered. Observations are made with a Zeiss monocular, monobjective, compound microscope with magnifications 56× and 160×. Photomicrographs are taken with a Leica camera Model II and Kodak Tri-X film. Pulmonary arterioles, pulmonary capillaries and pulmonary venules with active blood flows have been observed. Some unidentified vessels, which may be bronchial vessels, have also been seen.

**Blood Pressure Changes in the Monkey during Positive Acceleration.** R. W. LAWTON, M.D., L. GREENE, R. CROSBIE, and L. PETERSON, M.D. (Dept. of Physiology, University of Pennsylvania and U. S. Naval Air Development Center, Johnsville, Pa.). Anesthetized monkeys were exposed to sinusoidal positive accelerations of approximately 5 seconds' duration. Arterial blood pressure measurements were made at a variety of intraarterial sites by means of catheters and capacitance and strain gauge manometers. The hydrostatic forces between two arterial sites could be evaluated by subtracting diastolic blood pressure response curves. In experiments in which a catheter was moved in steps through the aorta, the actual and calculated catheter movement agreed to within ±0.5 cm. Step-wise movement of the catheter through the aorta resulted in a family of blood pressure responses,

showing a gradual progression from the striking blood pressure fall in the region of the aortic arch to a biphasic response in the region of the bifurcation. The biphasic response consisted of a transient increase in pressure of about 3.5 seconds' duration, followed by a fall in blood pressure below normal near the end of the acceleration. The blood pressure responses in the arterial system are believed to arise from hydrostatic effects which are opposed by a diminution in the volume of the arterial tree.

# BOOK REVIEWS AND NOTICES

ENDOKRINOLOGISCHE PSYCHIATRIE. By PROF. M. BLEULER, Professor of Psychiatry, Zurich University. Pp. 498; 30 ills. Stuttgart: Georg Thieme Verlag, 1954 (Intercontinental Medical Book Corporation, New York, U. S. Agents). Price, DM 46.50.

THIS is a new text that should prove interesting and useful. The author, a psychiatrist, has presented his own experience and a critical review of facts and opinions from the literature (there are over 2700 references) on the role of endocrine factors in psychic disorders. After an introduction on objectives, basic principles and limitations, there are sections on general considerations, on the psychopathology of the various endocrine disturbances and on the endocrinology of specific psychoses. The coverage is thorough and sound; the book is recommended to internists and psychiatrists who read German. R. K.

---

PROGRESS IN ALLERGY, VOLUME IV. Edited by PAUL KALLÓS, Helsingborg, Sweden. Pp. 520; 149 ills. Boston: Little, Brown & Co., 1955. Price, $20.00.

THIS volume contains chapters on various aspects of allergy by writers who are recognized authorities in their fields. The topics covered in this volume include Histology of Allergic and Related Lesions; Group Sensitization to Compounds of Quinone Structure and Its Biochemical Basis and the Role of these Substances in Cancer; Delayed Hypersensitivities; The Biosynthesis of Adrenal Steroids; Functional Interrelationships between the Anterior Pituitary and Adrenal Cortex in Intermediary Metabolisms; The Mechanisms of Action of Adrenal Cortical Hormones in Allergy; New Contributions to Experimental Asthma; and Respiratory Allergy to Fungus Spores. While much of the material is on the investigative aspects, there are obvious clinical associations. All allergists should have this book. R. K.

---

DAS TRANSVERSALE SCHICHTVERFAHREN. By DR. MED. ALFRED GEBAUER AND DR. MED. ALFRED SCHANEN. Pp. 313; 469 ills. Stuttgart: Georg Thieme Verlag, 1955. Price, $23.20.

THE rapid development and increasing usefulness of the planographic technique in diagnostic radiology is amply set forth in this very excellent volume. Even those who are unable to read German with any fluency can nevertheless benefit from the 469 illustrations documenting the case reports. Not only have the pictures been beautifully reproduced but many of them are overlaid with cellophane transparencies carrying captions and schematic outlines. The volume is a triumph of the bookmaker's art. R. K.

---

CHRISTOPHER'S MINOR SURGERY. Edited by ALTON OCHSNER, M.D., F.A.C.S., William Henderson Professor of Surgery and Chairman of the Department of Surgery, Tulane University of Louisiana School of Medicine, and MICHAEL E. DEBAKEY, M.D., F.A.C.S., Professor of Surgery and Chairman of The Department of Surgery, Baylor University College of Medicine. 7th ed. Pp. 547; 251 ills. Philadelphia and London: W. B. Saunders Co., 1955. Price, $9.00.

THE excellence of this edition is a reflection of the experience and interest of the editors. Much of the material contained in the book is prepared by a number of contributors, but most of the disadvantages of multiple authorship have been avoided since, for the most part, the collaborators are closely associated with the editors and continuity of thought is thus maintained with a minimum of repetition. The contents are very nicely arranged. The book ranges easily from the philosophical to the didactic. One of the most interesting and best written chapters is that entitled, "The Surgical Resident," by Dr. Frederick Fitzherbert Boyce. This should be read by every surgical resident or prospective surgical resident, and would surely be of interest to any practicing surgeon. This chapter alone is worth the price of the book. The book contains a remarkable variety of material. There are excellent illustrations, many of which are diagrammatic. One might complain of the paucity of detail concerning certain subjects, but I have, on many occasions, seen less material in much larger volumes. This book will prove tremendously valuable to the intern, the resident and the practitioner. G. R.

TEXTBOOK OF PHYSIOLOGY. Edited by JOHN F. FULTON, M.D., Yale University School of Medicine. 17th Ed. Pp. 1275; 600 ills. Philadelphia: W. B. Saunders Co., 1955. Price, $13.50.

THIS is a new edition of an excellent text. Improvements have been made in many sections and some previously rather difficult areas have been clarified and simplified. The section on nervous system is again an outstanding presentation which furnishes a basic concept for understanding the physiology of the nervous system. Illustrations and diagrams are extremely well chosen. A new chapter on the limbic system has recognized the importance of this area.

Blood coagulation is brought up-to-date and well presented in the light of modern concepts. Circulation is still an outstanding section and hemodynamics is simplified and improved. One wonders if it would not have been an advantage for the uninitiated medical student to have had the widely accepted ideas of Wilson presented along with the equally important ones of Nahum and Hoff in electrocardiography.

Another section which is much improved is that on secretory mechanisms under gastroenterology. Material on motility still leaves something to be desired.

The book will be a welcome addition to the library of medical students and those in related fields. M. O.

---

PERIPHERAL VASCULAR DISEASES. By E. V. ALLEN, M.D., N. W. BARKER, M.D., AND E. A. HINES, JR., M.D., Mayo Foundation, Graduate School, University of Minnesota. 2d ed. Pp. 825; 316 ills. Philadelphia: W. B. Saunders Co., 1955. Price, $13.00.

THE first edition, published in 1946, was the best text in the field of peripheral vascular diseases. It is gratifying that this second edition, now available, re-establishes its excellence.

The recent surgical advances in the treatment of occlusive disease of the aortic bifurcation are well covered by new sections on aortography and surgical technique. There are also new presentations of other subjects: coarctation of the aorta, hypertensive ischemic ulcers of the leg, techniques of sympathectomy, nonvascular operation for intermittent claudication, surgical treatment of varices, aortic aneurysms and vascular injuries.

The approach to all the subjects is a practical one based on wide clinical experience and sound conservative judgment. This book can be heartily recommended to all physicians. It is indispensable to the specialist in cardiovascular diseases. N. L.

---

ION EXCHANGE AND ADSORPTION AGENTS IN MEDICINE. THE CONCEPT OF INTESTINAL BIONOMICS. By GUSTAV J. MARTIN, SC.D., Research Director, National Drug Company. Pp. 333; 26 ills. Boston: Little, Brown & Company, 1955. Price, $7.50.

SINCE the application of anion exchange resins for the reduction of gastric acidity and cation exchange resins for the removal of sodium, to which the author has contributed greatly, there is increasing interest in the development and use of these cross-linked polymers to remove specific substances by selective adsorption. Pharmaceutical and biological agents may be purified, water softened, antibodies detected, gastric acidity determined without intubation, and sodium and other ions removed. Indeed, because of cation exchangers, milk is now available with 50 rather than 500 mg. per liter. The list of uses continues to grow and it is necessary to become acquainted with the nature of these substances. In this text, the chemistry and medical application of anion and cation exchange resins are clearly presented. Also, there are chapters concerned with the chemistry and application of other compounds that may be used to remove specific ions or substances, such as the chelators, the nonresinous ion exchangers and other adsorption materials like charcoal, kaolin and alginic acid. Consideration is given to the possibility of conditioning by these substances the intestinal tract to allow for absorption of beneficial substances and retention in the intestine of the insoluble useless or toxic residue. By this method, the author contends, chronic degenerative disease may be prevented. J. Z.

---

PROGRESS IN STEREOCHEMISTRY. VOL. 1. Edited by W. KLYNE, M.A., B.SC., PH.D., Reader in Biochemistry, University of London. Pp. 378; 52 ills. New York: Academic Press, Inc. (London: Butterworth Scientific Publications), 1954. Price, $8.00.

ALTHOUGH this book surveys the wide fields of physical, inorganic and organic chemistry as well as biological chemistry, it should be of interest to those who contemplate a consideration of the molecular basis of biology.

The orientation and structure of physiologically important substances such as the proteins and carbohydrates, and others, and their constituent parts is considered along with reaction mechanisms based on stereochemical configurations. The authors of the various chapters are active workers in the field about which they write. Nine are associated with universities or hospitals in Great Britain; two are from Australia and one is from the United States.

The chapter headings with the authors are: 1. The Shape of Simple Molecules by A. D. Walsh; 2. The Conformations of Six-membered Ring Systems by W. Klyne; 3. Stereochemical Factors in Reaction Mechanisms and Kinetics by P. B. D. de la Mare; 4. The Relationships Between the Stereochemistry and Spectroscopic Properties of Organic Compounds by E. A. Braude and E. S. Waight; 5. The Correlation of Configurations by J. A. Mills and W. Klyne; 6. The Stereochemistry of the Hydrogen Bond by L. Hunter; 7. The Stereochemistry of Compounds of High Molecular Weight by E. J. Ambrose; 8. The Stereospecificity of Enzyme Reactions by V. P. Whittaker; 9. The Stereochemistry of Complex Compounds by R. S. Nyholm; Appendix: Bond Length and Valency Angles by Allan Maccoll. R. B.

---

Rutin and Related Flavanoids: Chemistry, Pharmacology, Clinical Application. By John Q. Griffith, Jr., M.D., John Q. Griffith Research Foundation, Philadelphia; Charles F. Krewson, Ph.D. and Joseph Naghski, Ph.D., Eastern Utilization Research Branch, Agricultural Research Service, United States Department of Agriculture, Philadelphia. Pp. 275; 44 ills. Easton, Pa.: Mack Publishing Company, 1955. Price, $7.50.

The junior authors are part of a team responsible for the isolation of rutin from tobacco in 1941. The next year, the senior author was the first to test the capacity of rutin to correct capillary fault primarily in individuals with hypertension. This book summarizes their experience and comprehensively reviews the world's literature on rutin. The bibliography contains 803 references each of which is specifically quoted in the text. This book may be used as a reference for all work related to rutin up to the time of publication.

The first chapter is devoted to the chemistry and manufacture of rutin. The next three chapters are concerned with capillary physiology, permeability and fragility. These chapters are followed by one on the pharmacology of rutin. This reviewer is unable to understand the authors' distinction between the alleged physiologic and pharmacologic effects of rutin. There is no clear distinction made between the effects of peroral and parenteral modes of administration.

The last half of the book is devoted to the clinical usefulness of rutin. Considerable space is devoted to criticising reports unfavorable to rutin. Criticisms are based upon 1) inadequate dosage 2) inadequate duration of treatment or 3) erroneous statistical methodology. The effect of this criticism is completely shattered by the blind acceptance of favorable reports regardless of duration of treatment or dosage. Thus, favorable effects are reported on self limiting or episodic hemorrhagic disturbances such as allergic purpura, angioneurotic edema, drug idiosyncrasy, rheumatic fever, telangiectasis, pulmonary apoplexy and others.

The senior author's interest in rutin is based upon the theory that skin capillary fault, as measured only by the Göthlin test, is related to cerebral hemorrhage of hypertensive origin and is correctable by rutin. The evidence for the effectiveness of this treatment is given in references 281, 282, 283, 285 and 286. L. S.

---

Surgery of the Small and Large Intestine. By Charles W. Mayo, M.D., Section of Surgery, Mayo Clinic, Rochester, Minnesota; Professor of Surgery, Mayo Foundation, Graduate School, University of Minnesota. Pp. 340; 94 ills. Chicago: The Year Book Publishers, Inc., 1955. Price, $9.00.

This is the latest of the handbooks of operative surgery, under the authorship of Charles W. Mayo. Doctor Mayo, the son of one of the founders of the Mayo Clinic, is Professor of Surgery, Mayo Foundation, Graduate School, at the University of Minnesota. The handbook is very concisely done in 340 pages. It contains 94 excellent illustrations by the head of the Mayo Clinic Art Studio, Mr. Russell Drake. If the book contained nothing but these very beautiful and accurate illustrations, it would be a worthwhile volume. In his Preface, Doctor Mayo states that, "The purpose of this book is to present to those interested concise descriptions and illustrations of the more common surgical procedures performed for lesions of the small

and large intestine, including the rectum." He accomplishes this purpose admirably. The book is divided into four sections. The first section discusses diet, surgical instruments, and incisions. The second section discusses the small intestine, beginning with the duodenum, on through the jejunum to the ileum, and then gives a brief discussion of obstruction in the small intestine. Section III discusses the colon: anatomy, pre-and post-operative care, surgical treatment of benign and malignant lesions, as well as the use of colostomy. Various surgical techniques are briefly covered. Section IV covers the rectum and anus.

This book should be especially valuable to the young surgeon. It is surely not to be used as a complete reference book. G. R.

---

PERIPHERAL NERVE INJURIES. BY THE NERVE INJURIES COMMITTEE OF THE MEDICAL RESEARCH COUNCIL OF GREAT BRITAIN. Special Report Series No. 282. Edited by H. J. SEDDON. Pp. 451; 276 ills., 122 tables. London: Her Majesty's Stationery Office, 1954. Price, 2 pounds, 15 shillings.

THIS report consists of a series of studies by those chiefly responsible for the day-to-day work of five nerve injuries centers during and following the Second World War. It is concerned, therefore, only with those advances in the understanding of nerve injuries made by the British workers during the war years.

The contents are divided into ten chapters, many of them written by different investigators.

There is a wealth of data in this book that is indispensable to those treating peripheral nerve injuries.

It is, therefore, most valuable as a reference work and guide to those who specialize in this field. M. S.

---

HANDBOOK OF RADIOLOGY. Edited by RUSSELL H. MORGAN, M.D., Professor of Radiology, Johns Hopkins University, and KENNETH E. CORRIGAN, PH.D., Associate Professor of Radiology, Wayne University. Pp. 518; illustrated. Chicago: Year Book Publishers, Inc., 1955. Price, $10.00.

THIS handbook is primarily a compilation of the physical data, in the form of tables and graphs, used in modern medical radiology. The editors have had the assistance of a distinguished group of collaborating radiologic physicists and clinical radiologists. There are sections covering definitions of physical terms and units, conversion tables and formulae, radiotherapeutic data, data on isotopes, radiography and fluoroscopy, and protection. A vast amount of factual material has been assembled here in one compact volume for the first time. It will be very useful to anyone involved more than superficially in the medical applications of ionizing radiations.

H. S.

---

THE ADOPTED BREAK SILENCE. Compiled and written by JEAN M. PATON, M.A., M.S.W. Pp. 180; 3 ills. Philadelphia: Life History Study Center, 1954. Price, $3.00.

THIS special study, rather well titled, puts on record the views and attitudes of adults who were once adopted children. The book is representative of the change in attitude toward adoption. It has now become frequent and accepted whereas 50 years ago it was surrounded with more secrecy, misgiving and potential emotional distress for both the adopted and his new parents.

There is a wealth of factual and psychological information in this small book about various facets of the adoption problem. Considerable space is given to the curiosity of the adopted about his natural parents and how this may be dealt with. The philosophy of the book tends to favor helping the adopted individual to find out as much as possible about his background if and when he is able to deal with it constructively. Obviously this would be a matter of careful judgment by those guiding his growth and development. Recommended for the physician and social worker having anything to do with adoption.

O. E.

---

HEALTH SUPERVISION OF YOUNG CHILDREN: A GUIDE FOR PRACTICING PHYSICIANS AND CHILD HEALTH CONFERENCE PERSONNEL. Prepared and authorized for publication by the Committee on Child Health of the American Public Health Association. Pp. 179. New York: American Public Health Association, Inc., 1955. Price, $2.00 plus postage.

THIS is an extremely well-planned, intelligently written book presenting a mature approach to the newer concepts of child health. Not only does the book offer practical information to physicians concerned with the management of child health conferences, but the sections dealing with physician-patient,

and physician-family relationships could well be read with profit by all physicians and students. It is seldom that material dealing with such intangibles as these is presented in such a readable manner and covers so adequately these more profound concepts of medicine and pediatrics. Fortunately, too, this book appears at a most opportune time when the pediatric approach to the problem of over-all child health care is undergoing change.

The style of presentation of material is unique, easy to comprehend, and yet retains the profoundness of its message. The book is so well arranged that material relative to the practical management of child health conferences can be omitted by readers not particularly concerned with this problem.

The publication of this book is the result of the finest type of inter-disciplinary group effort. All of its participants should be justly proud. R. O.

---

## NEW BOOKS

*Laboratory Techniques in Rabies.* WHO Monograph Series No. 23. By Various Authors. Pp. 150; 51 ills., including 1 color plate. Geneva: World Health Organization, 1954. Price, $3.00.

Prepared by fourteen outstanding research workers in the field of rabies, this monograph will some day become the authoritative text on internationally applicable rabies laboratory techniques. There are presented papers on laboratory diagnosis, methods of vaccine production, vaccine potency, production of hyperimmune serum and the growing and breeding of experimental animals. There have been selected procedures that would be dependable and practical without sacrificing minimal standards and at the same time adaptable to the limited facilities and personnel of rabies laboratories the world over. The illustrations are numerous and good and there are adequate references to source material. R. K.

---

*Diabetes Mellitus: Objectives and Methods of Treatment.* By Henry T. Ricketts, M.D., Professor of Medicine, University of Chicago School of Medicine. Pp. 123; 13 ills. Springfield, Ill.: Charles C Thomas, 1955. Price, $3.25.

Among the many schema that have appeared for the treatment of diabetes mellitus there are few that equal the simplicity and practicality of the methods outlined in this manual. The initial chapter deals with the objectives to be sought in the treatment of this disease. It would be well for all physicians engaged in the management of diabetic patients to thoroughly comprehend this presentation. The reviewer subscribes enthusiastically to the programs of careful metabolic control which are skillfully and concisely detailed for the reader. The emphasis on the fractional urine glucose determination by the patient and other details of follow-up care for the various clinical types of diabetes provide excellent guides for the practitioner engaged in the treatment of this disease. The management of the diabetic during episodes of coma and acidosis is outlined and follows more or less conventional methods. The fourth section deals with the management of the surgical diabetic using the 6 hourly schedule of insulin and glucose administration during the operative period. The use of depot insulin currently recommended by many clinics during the period of surgical intervention is not presented. The final section is devoted to the diabetic diet for which the popular food exchange system is used and is presented in detail including all of the recommended sample meal plans at various caloric levels. The manual deserves to be read by all medical students and physicians at any level who are interested in the treatment of diabetes mellitus. C. S.

---

*The Colon: Its Normal and Abnormal Physiology and Therapeutics.* (Ann. New York Acad. Sci., 58, Art. 4, pp. 293–540). By M. L. Tainter, Thomas P. Almy and others. Pp. 247; illustrated. New York: New York Academy of Sciences, 1954. Price, $4.50.

A symposium on the function of the colon, its diseases and their treatment is presented in four sections of five to seven papers and a panel discussion each on Physiology and Pharmacology, Etiology of Colonic Disorders, Pharmacology of the Abnormal Colon, and The Treatment of Colonic Disorders. R. K.

---

*Biology of Anopheles Gambiae.* WHO Monograph Series No. 9. By M. H. Holstein. Pp. 172; 22 ills. Geneva: World Health Organization, 1954. Price, $2.00.

This monograph records the investigations into the biology of this important vector of disease. The study was sponsored by the World Health Organization. R. K.

---

*Tissue Culture Technique in Pharmacology.* C. M. Pomerat (University of Texas, Medical Branch), Consulting Editor. Ann. New York Acad. Sci., V. 58, Art. 7. Pp. 971–1326; 215 ills. New York: The New York Academy of Sciences, 1954. Price, $4.50.

At a conference sponsored by the New York Academy of Sciences and the Tissue Culture Society, fifty scientists from Belgium, England, Germany, France, and the United States presented a series of twenty-seven papers which comprise this report. The work is divided into three parts: *Part I.* Pure strain, long-term and mass culture methods. Commercial and synthetic media. Virology. *Part II.* Special assay technique: comparison between *in vitro* and *in vivo* results.

*Part III.* The actions of chemical agents on cell organoids and mitosis. While the work will be of value primarily to those engaged in research involving tissue culture methods, it should also have considerable appeal and instructive value for anyone engaged in research in cancer, pharmacology, or virology. Several of the papers will be of particular interest to the biochemist and at least one, on topical medicaments, should interest the dermatologist. R. S.

---

*Drugs in Current Use, 1955.* Edited by WALTER MODELL, M.D., Associate Professor of Clinical Pharmacology, Cornell University Medical College. Pp. 147 New York: Springer Publishing Co., Inc., 1955. Price, $2.00.

A CONVENIENT pocket-size book that answers any doctor's questions about drugs currently in common use. It is the intention of the publisher to keep the volume up-to-date by annual revisions. R. K.

---

*Behringwerk-Mitteilungen, Heft 29. Hunddertjahrfeier de Geburtstage von Paul Ehrlich und Emil von Behring in Frankfurt-Main, Marburg-Lahn und Hoechst.* Pp. 127; illustrated. Marburg: Universitäts-und Verlagsbuchhandlung, 1954.

A RECORD of the proceedings of the centennial celebration of the birthdays of Paul Ehrlich and Emil von Behring in Frankfurt, Marburg and Hoechst in March, 1954; also the addresses of the recipients of the Emil von Behring Prize: in 1948, Hans Schmidt, Marburg, Germany; 1952, Sir MacFarlane Burnet, Melbourne, Australia; and 1954, Michael Heidelberger, New York City. R. K.

---

*Der Scharlach und seine Behandlung.* BY DR. MED. W. PULVER. Pp. 220; 9 ills. Bern: Verlag Hans Huber, 1954. Price, DM 19.80.

AN excellent monograph presenting the background and current status of our knowledge of scarlet fever, with an adequate survey of the world's literature on the subject. Clinicians who read German will find it an excellent text. R. K.

---

*Rabies. Bulletin of the World Health Organization, Vol. 10, No. 5, 1954.* Pp. 164; 12 ills. Geneva: World Health Organization, 1954. Price, $1.50.

THIS is an important collection of articles dealing with the significant advances in the field of rabies. It begins with the adaptation of rabies virus in chicks and developing chick embryos, continues with the control of rabies in animals. There are reports from various parts of the world including the United States, Malaya, Southern Rhodesia, Austria, Canada and Latin America. The next group of papers deals with the prevention of human rabies, and offers some important data on the improvement of prophylaxis by the use of antiserum and some experimental observations on the value of wound prophylaxis with caustics, soap solutions and detergents. Each article has a summary in French. The book is highly recommended. R. K.

---

*Any Questions?* Pp. 227. London: British Medical Association House, 1954. Price, 7 s. 6 d.

FROM the department "Any Questions" of the British Medical Journal, the Editor of that publication has again selected a number of questions and their answers ranging from a few lines to several pages, and touching on all fields of clinical medicine. In addition, the volume presents a cumulative index for all three books which have appeared to date. Its practical nature and its convenient pocket size recommend this little volume to all physicians. R. K.

---

*Biologisch-Medizinisches Taschenjahrbuch, 1955.* BY DR. MED. HANS HAFERKAMP. Pp. 626. Stuttgart: Hippokrates-Verlag, 1955. Price, DM 5.

---

*The Status of Multiple Sclerosis.* BY HAROLD R. WAINERDI AND TWENTY-EIGHT OTHER INVESTIGATORS. Ann. New York Acad. Sci., Vol. 58, Art. 5. Pp. 180; illustrated. New York: New York Academy of Sciences, 1954. Price, $4.50.

---

*Properties of Surfaces.* BY CECIL V. KING AND TWENTY OTHER AUTHORITIES. Ann. New York Acad. Sci., Vol. 58, Art. 6. Pp. 250; illustrated. New York: New York Academy of Sciences, 1954. Price, $3.50.

---

*Time Distortion in Hypnosis.* BY LINN F. COOPER, M.D., AND MILTON H. ERICKSON, M.D. Pp. 191; 8 ills. Baltimore: Williams & Wilkins Co., 1954. Price, $4.00.

HERE is an account of many interesting experiments in time distortion in hypnosis with an attempt to interpret the findings and some case histories which illustrate possible clinical uses of the method. Under moderately deep hypnosis the investigators suggest to the subject that he will perceive a short interval of time as for instance ten seconds as a long interval of ten to 30 minutes. The subjects accept this suggestion and feel as though they have been in hypnosis for long intervals of time. Apparently then, in five or ten seconds, they can accomplish mental work which ordinarily requires ten or 30 minutes which they believe has elapsed. "Thought, under time distortion, while appar-

ently proceeding at a normal rate from the subject's point of view, can take place with extreme rapidity relative to world time. Such thought may be superior, in certain respects, to waking thought. There is some evidence that the recovery of material from the unconscious can be facilitated." Evidently creative thought, motor learning and other types of learning can be facilitated. Solving of mathematical problems allegedly cannot.

Clinically the method was used to enable the patient to recall long, involved and multiple memories in a very brief period of time.

By way of criticism it would appear that the authors did not have much comprehension of the psychodynamic implications of their work.

O. E.

---

*Probleme und Beispiele Biologischer Regelung.* By Prof. Dr. R. Wagner, Munich. Pp. 219; 38 ills. Stuttgart: Georg Thieme Verlag, 1954 (Intercontinental Medical Book Corporation, New York, U. S. Agents). Price, $7.00.

A physiologist speculates in a challenging and interesting fashion on certain regulating mechanisms, particularly those involved in voluntary movement and those concerned in the circulation of the blood. Physiologists and clinicians concerned with these fields will find the volume instructive if they read German.

R. K.

---

*1955 Medical Progress. A Review of Medical Advances During 1954.* Edited by Morris Fishbein, M.D. Pp. 346. New York: The Blakiston Division, McGraw-Hill Book Company, Inc., 1955. Price, $5.00.

This book is a presentation of the medical news of the year, expertly edited by Dr. Fishbein. Its popularity is indicated by its appearance for the third successive year. Outstanding authorities report various articles culled from the current literature of their particular specialty. This year, chapters on urology, gynecology, psychology and rehabilitation are omitted. Diseases of the chest, omitted last year, are given again and a new chapter, Diabetes by Dr. Joslin, appears. Surgery is reviewed by Dr. Judd instead of Dr. Mayo and Cardiovascular Diseases by Dr. Bay instead of Dr. White. Discussion is brief. Indeed, critical analysis is often wanting However, a text like this one fills an important need, for it allows for dissemination of knowledge of medical advances. It is necessary reading not only for the general practitioner but also for the specialist who may have neglected the literature of other fields of medicine.

J. Z.

---

*The Year Book of Neurology, Psychiatry and Neurosurgery.* Edited by Roland P. Mackay, M.D., Professor of Neurology, University of Illinois (Neurology); S. Bernard Wortis, M.D., Professor of Psychiatry and Neurology, New York University (Psychiatry); Percival Bailey, M.D., Distinguished Professor of Neurology and Neurological Surgery, University of Illinois and Oscar Sugar, M.D., Associate Professor of Neurological Surgery, University of Illinois (Neurosurgery). Pp. 619; 97 ills. Chicago: Year Book Publishers, Inc., 1955. Price, $7.00.

This little handbook maintains its excellence every year. The contents are well balanced between Neurology, Psychiatry and Neurosurgery and include adequate abstracts of interesting and important articles that were published in these fields during the years 1953 and 1954.

The printing is easy to read and the illustrations are clear. It is a must for all interested in any facet of Neurology, Psychiatry or Neurosurgery.

M. S.

---

*Prerequisites of Good Teaching and Other Essays.* By Dr. Ernest Sachs, Research Associate in Surgery and Medical History, Yale University. Pp. 118; 1 ill. Hamden, Conn.: The Shoe String Press, 1954. Price, $2.50.

The author has culled from his thirty-five years of clinical medical teaching a dozen lectures that can be read with profit by all young teachers and students. Here are some of the titles: The Prerequisites of Good Teaching, The Importance of Getting a Thorough Training, Private Practice versus "Full Time," Conducting a Clinic, The Question of Fees, The Technique of Obtaining an Autopsy, Telling the Family of the Seriousness of an Illness, Comforting a Family in Difficult Situations, The Case that is Diagnosed Too Late, and Keeping Patients with a Hopeless Condition Alive. It is a pity that this little book is so expensive.

R. K.

---

## NEW EDITIONS

*Modern Treatment Yearbook, 1955.* Edited by Sir Cecil Wakeley, Bt., K.B.E., C.B. 21st ed. Pp. 344; 45 ills. London: Bailliere, Tindall & Cox, Ltd., 1955 (Williams & Wilkins Company, Baltimore, U. S. Agents). Price, $6.00.

This is the twenty-first edition since the first in 1934. The book includes 36 chapters on various aspects of clinical medicine, written by teachers and specialists in their respective fields. The subject matter is well presented, concise and particularly adapted to the use of the general practitioner. The fact that the drug names and doses conform to the British pharmacopoeia offers no real drawbacks.

R. K.

---

*Communicable Diseases.* By Franklin H. Top, A.B., M.D., M.P.H., Professor of Hygiene and Preventive Medicine, State University of Iowa, and Collaborators. 3rd ed. Pp. 1208; 109 ills. and 15 color plates. St. Louis: C. V. Mosby Co., 1955. Price, $18.50.

ALL physicians will welcome the appearance of the third edition of this excellent work. Its excellent presentation of clinical pictures of communicable diseases, its fine color photographs, its numerous references to the literature and its excellent index were features established in previous editions. Striking changes have occurred in this field in the eight years that have passed since the appearance of the last edition. The author and his twenty-four collaborators are to be congratulated on their thorough revision of the text and the inclusion of much new material.

R. K.

---

*A Primer of Electrocardiography.* By GEORGE E. BURCH, M.D., Henderson Professor of Medicine, Tulane University, and TRAVIS WINSOR, M.D., Assistant Clinical Professor of Medicine, University of Southern California. 3rd. ed. Pp. 286; 281 ills. Philadelphia: Lea & Febiger, 1955. Price, $5.00.

STUDENTS, practitioners and teachers will welcome this third edition of an extremely useful book. The presentation is simple, concise and practical, well adapted not only to the beginning student but to the general physician who wishes to keep informed on the essentials of this subject. The text has been brought up-to-date and the numerous excellent illustrations also include some new ones. The book is heartily recommended.

R. K.

---

*Introduction to Parasitology with Special Reference to the Parasites of Man.* By ASA C. CHANDLER, M.S., PH.D., Professor of Biology, Rice Institute, Houston Texas. 9th ed. Pp. 799; 257 ills. New York: John Wiley & Sons, Inc. London: Chapman & Hall, Ltd., 1955. Price, $8.50.

TEACHERS, students and practitioners will welcome the 9th edition of this highly successful text, a leader in its field since its first appearance in 1918. It represents a thorough revision and contains much new material, with emphasis on parasitic diseases of increasing current interest in the world, such as leptospirosis, schistosomiasis, amebiasis and others. There are adequate references to the important recent literature. The illustrations include many excellent drawings.

R. K.

---

**THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES**

*Published Monthly. Illustrated.*

*Subscription price: 1 year $10.00; 2 years $18.00.*
*(One year subscription to Canada, South and Central America, Philippines and Spain, $10.36; all other countries $11.14.)*

All foreign subscriptions payable in advance in United States dollars.

Business Correspondence: Lea & Febiger, 600 S. Washington Sq., Philadelphia 6, Pa.

---

**NOTICE AND INSTRUCTIONS TO CONTRIBUTORS**

MANUSCRIPTS intended for publication in THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES, and correspondence should be sent to the Editor:

DR. RICHARD A. KERN, Temple University School of Medicine, Philadelphia 40, Pa.

Articles are accepted for publication in THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES exclusively, except in the case of subsequent publication in Society proceedings.

MANUSCRIPTS should be typewritten on one side only, of good quality paper and should be double spaced with liberal margins. The author's chief position and, when possible, the Department from which the work is produced should be indicated in the subtitle.

Each article should have a summary which gives the essential point and purpose of the paper. This summary will be translated into INTERLINGUA for the benefit of our foreign readers.

ILLUSTRATIONS accompanying articles should be numbered and have typed captions bearing corresponding numbers. For identification they should also have the author's name written on the margin or back. Line drawings and charts should be prepared with black India ink. Special arrangements can be made for printing color plates, elaborate tables or an excessive number of illustrations.

The recommendations of the American Medical Association Style Book should be followed.

REFERENCES should be numbered and at the end of the articles arranged alphabetically according to the name of the first author and should be complete, that is, author's name, journal, volume, page and year (in Arabic numbers).

RETURN POSTAGE should accompany all manuscripts but will be returned to the author if the manuscript is accepted.

100 REPRINTS will be supplied gratis. Covers will be omitted on all articles. Orders of additional reprints will be supplied in multiples of 100. An order form showing cost of reprints is sent with proof. Individual reprints can usually be obtained by writing directly to the author.